ENDOTHELIN ANTAGONISTS

This application is a continuation-in-part application of U.S. patent application Serial No. 09/634, 661, filed August 7, 2000, which is a continuation-in-part application of U.S. patent application Serial No. 09/048,955, filed March 27, 1998, which is a continuation-in-part application of U.S. patent application Serial No. 08/794,506, filed February 4, 1997 which is a continuation-in-part of U.S. patent application Serial No. 08/600,625, filed February 13, 1996, which is a continuation-in-part of U.S. patent application Serial No. 08/497,998, filed August 2, 1995, which is a continuation-in-part of U.S. patent application Serial No. 08/442,575, filed May 30, 1995, which is a continuation-in-part of U.S. patent application Serial No. 08/334,717, filed November 4, 1994, which is a continuation-in-part of U.S. patent application Serial No. 08/293,349, filed August 19, 1994.

Technical Field

The present invention relates to compounds which are endothelin antagonists, processes for making such compounds, synthetic intermediates employed in these processes, methods and compositions for antagonizing endothelin, methods for the inhibition of bone metastases, methods for the prevention of growth of new metastases, methods for the inhibition of bone turnover, and methods for the prevention of bone loss in patients, including cancer patients, using an endothelin ET receptor antagonist.

Background of the Invention

Endothelin (ET) is a 21 amino acid peptide that is produced by endothelial cells. ET is produced by enzymatic cleavage of a Trp-Val bond in the precursor peptide big endothelin (Big ET). This cleavage is caused by an endothelin converting enzyme (ECE). Endothelin has been shown to constrict arteries and veins, increase mean arterial blood pressure, decrease cardiac output, increase cardiac contractility in vitro, stimulate mitogenesis in vascular smooth muscle cells in vitro, contract non-vascular smooth muscle including guinea pig trachea, human urinary bladder strips and rat uterus in vitro, increase airway resistance in vivo, induce formation of gastric ulcers, stimulate release of atrial natriuretic factor in vitro and in vivo, increase plasma levels of vasopressin, aldosterone and catecholamines, inhibit release of renin in vitro and stimulate release of gonadotropins in vitro.

It has been shown that vasoconstriction is caused by binding of endothelin to its receptors on vascular smooth muscle (Nature 332 411 (1988), FEBS Letters 231 440 (1988) and Biochem. Biophys. Res. Commun. 154 868 (1988)). An agent which suppresses endothelin production or an agent which binds to endothelin or which inhibits the binding of endothelin to an endothelin receptor will produce beneficial effects in a variety of therapeutic

areas. In fact, an anti-endothelin antibody has been shown, upon intrarenal infusion, to ameliorate the adverse effects of renal ischemia on renal vascular resistance and glomerular filtration rate (Kon, et al., J. Clin. Invest. 83 1762 (1989)). In addition, an anti-endothelin antibody attenuated the nephrotoxic effects of intravenously administered cyclosporin (Kon, et al., Kidney Int. 37 1487 (1990)) and attenuated infarct size in a coronary artery ligation-induced myocardial infarction model (Watanabe, et al., Nature 344 114 (1990)).

Clozel et al. (Nature 365: 759-761 (1993)) report that Ro 46-2005, a nonpeptide ET-A/B antagonist, prevents post-ischaemic renal vasoconstriction in rats, prevents the decrease in cerebral blood flow due to subarachnoid hemorrhage (SAH) in rats, and decreases MAP in sodium-depleted squirrel monkeys when dosed orally. A similar effect of a linear tripeptide-like ET-A antagonist, BQ-485, on arterial caliber after SAH has also been recently reported (S.Itoh, T. Sasaki, K. Ide, K. Ishikawa, M. Nishikibe, and M. Yano, Biochem. Biophys. Res. Comm. , 195: 969-75 (1993). These results indicate that agents which antagonize ET/ET receptor binding will provide therapeutic benefit in the indicated disease states.

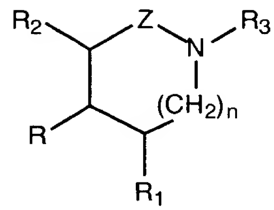
Agents with the ability to antagonize ET/ET receptor binding have been shown to be active in a number of animal models of human disease. For example, Hogaboam et al (EUR. J. Pharmacol. 1996, 309, 261-269), have shown that an endothelin receptor antagonist reduced injury in a rat model of colitis. Aktan et al (Transplant Int 1996, 9, 201-207) have demonstrated that a similar agent prevents ischemia-reperfusion injury in kidney transplantation. Similar studies have suggested the use of endothelin antagonists in the treatment of angina, pulmonary hypertension, Raynaud's disease, and migraine. (Ferro and Webb, Drugs 1996, 51,12-27).

Abnormal levels of endothelin or endothelin receptors have also been associated with a number of disease states, including prostate cancer (Nelson et al, Nature Medicine 1995, 1, 944-949) and as a modulator in osteoblastic bone lesion (UROLOGY 53:1063-1069, 1999). suggesting a role of endothelin in the pathophysiology of these diseases.

Wu-Wong et al (Lfe Sciences 1996, 58, 1839-1847) have shown that both endothelin and endothelin antagonists bind tightly to plasma proteins, e.g., serum albumin. This plasma protein binding can decrease the effectiveness with which the antagonists inhibit endothelin's action. Thus, endothelin antagonists with reduced plasma protein binding may be more effective than highly bound congeners.

Disclosure of the Invention

In accordance with the present invention there are compounds of the formula (I):



(I)

wherein

Z is $-C(R_{18})(R_{19})-$ or $-C(O)-$ wherein R_{18} and R_{19} are independently selected from hydrogen and loweralkyl;

n is 0 or 1;

R is $-(CH_2)_m-W$ wherein m is an integer from 0 to 6 and W is

(a) $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,

(b) $-PO_3H_2$,

(c) $-P(O)(OH)E$ wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

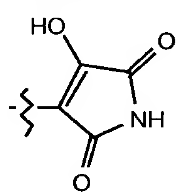
(i) hydroxy,

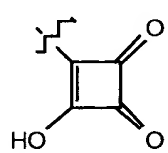
(j) alkoxy,

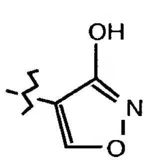
(k) sulfonamido,

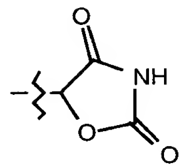
(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,

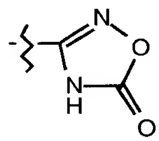
(m) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is defined as above,

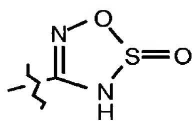
(n)  ,

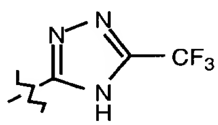
(o)  ,

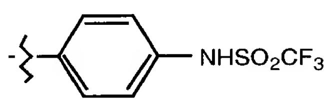
(p)  ,

(q)  ,

(r)  ,

(s)  ,

(t)  , or

(u)  ;

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N\text{-}R_{cc}$- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

R_3 is (a) R_4-C(O)-R_5-, R_4-R_{5a}- , R_4-C(O)- R_5-N(R_6)- , R_6-S(O)$_2$-R_7- or R_{26}-S(O)-R_{27}-

wherein R_5 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) -N(R_{20})-R_8- or -R_{8a}-N(R_{20})-R_8- wherein R_8 and R_{8a} are independently selected from the group consisting of alkylene and alkenylene and R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl or cycloalkylalkyl or (v) -O-R_9- or -R_{9a}-O-R_9- wherein R_9 and R_{9a} are independently selected from alkylene;

R_{5a} is (i) alkylene or (ii) alkenylene;

R_7 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or

(iv) $-N(R_{21})-R_{10}-$ or $-R_{10a}-N(R_{21})-R_{10}-$ wherein R_{10} and R_{10a} are independently selected from the group consisting of alkylene and alkenylene and R_{21} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R_4 and R_6 are independently selected from the group consisting of

(i) $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are independently selected from

(1) hydrogen,
(2) loweralkyl,
(3) haloalkyl,
(4) alkoxyalkyl,
(5) haloalkoxyalkyl,
(6) alkenyl,
(7) alkynyl,
(8) cycloalkyl,
(9) cycloalkylalkyl,
(10) aryl,
(11) heterocyclic,
(12) arylalkyl,
(13) (heterocyclic)alkyl,
(14) hydroxyalkyl,
(15) alkoxy,
(16) aminoalkyl,
(17) trialkylaminoalkyl,
(18) alkylaminoalkyl,
(19) dialkylaminoalkyl,
(20) carboxyalkyl, and
(21) diarylalkyl,

(ii) loweralkyl,
(iii) alkenyl,
(iv) alkynyl,
(v) cycloalkyl,
(vi) cycloalkylalkyl,
(vii) aryl,
(viii) arylalkyl,
(ix) heterocyclic,
(x) (heterocyclic)alkyl,
(xi) alkoxyalkyl,

(xii) hydroxyalkyl,

(xiii) haloalkyl,

(xiv) haloalkenyl,

(xv) haloalkoxyalkyl,

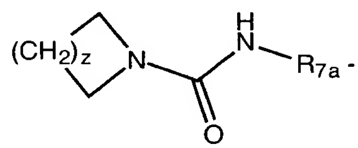
(xvi) haloalkoxy,

(xvii) alkoxyhaloalkyl,

(xviii) alkylaminoalkyl,

(xix) dialkylaminoalkyl,

(xx) alkoxy,



(xxi)

wherein z is 0-5 and R_{7a} is alkylene, and

(xxii) $(R_{11a})(R_{12a})N\text{-}N(H)\text{-}$

wherein R_{11a} and R_{12a} are independently selected from aryl and alkyl,

R_{26} is (i) loweralkyl, (ii) haloalkyl, (iii) alkenyl, (iv) alkynyl, (v) cycloalkyl, (vi) cycloalkylalkyl, (vii) aryl, (viii) arylalkyl, (ix) heterocyclic, (x) (heterocyclic)alkyl, (xi) alkoxyalkyl or (xii) alkoxy-substituted haloalkyl; and

R_{27} is alkylene or alkenylene;

(b) $R_{22}\text{-O-C(O)-}R_{23}\text{-}$ wherein R_{22} is a carboxy protecting group or heterocyclic and R_{23} is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $\text{-N(}R_{24}\text{)-}R_{25}\text{-}$ wherein R_{25} is alkylene and R_{24} is hydrogen or loweralkyl,

(c) loweralkyl,

(d) alkenyl,

(e) alkynyl,

(f) cycloalkyl,

(g) cycloalkylalkyl,

(h) aryl,

(i) arylalkyl,

(j) aryloxyalkyl,

(k) heterocyclic,

(l) (heterocyclic)alkyl,

(m) alkoxyalkyl,

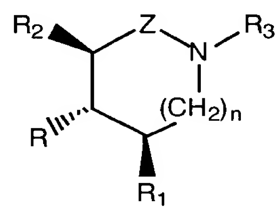
(n) alkoxyalkoxyalkyl, or

(o) R_{13}-C(O)-CH(R_{14})-

wherein R_{13} is amino, alkylamino or dialkylamino and R_{14} is aryl or R_{15}-C(O)- wherein R_{15} is amino, alkylamino or dialkylamino;

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the invention is a compound of formula (II)



(II)

wherein the substituents -R_2, -R and -R_1 exist in a *trans,trans* relationship and Z, n, R, R_1, R_2, and R_3 are as defined above.

Another preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0 and Z is -CH_2-.

Another preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 1 and Z is -CH_2-.

Another preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is -CH_2-, and R_3 is R_4-C(O)-R_5- , R_6-S(O)$_2$-R_7- or R_{26}-S(O)-R_{27}- wherein R_4, R_5, R_6, R_7, R_{26} and R_{27} are as defined above.

Another preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is -CH_2-, and R_3 is alkoxyalkyl or alkoxyalkoxyalkyl.

Another preferred embodiment of the invention is a compound of formula (I) or formula (II) wherein n is zero; Z is -CH_2- wherein R_{18} and R_{19} are hydrogen; R is C(O)-G wherein G is hydrogen; R_1 is aryl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R_2 is 1,3-benzodiox-5-yl; R_3 is R_4-C(O)-R_5- wherein R_5 is methylene and R_4 is selected from (R_{11})(R_{12})N- and (R_{11a})(R_{12a})N-N(H)-; one of R_{11} and R_{12} is hydrogen and the other is selected from arylalkyl and diarylalkyl wherein each

aryl group of the diarylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is aryl.

Another preferred embodiment of the invention is a compound of formula (I) or formula (II) wherein n is zero; Z is $-CH_2-$ wherein R_{18} and R_{19} are hydrogen; R is C(O)-G wherein G is hydrogen; R_1 is phenyl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R_2 is 1,3-benzodiox-5-yl; R_3 is R_4-C(O)-R_5- wherein R_5 is methylene and R_4 is selected from $(R_{11})(R_{12})N$- and $(R_{11a})(R_{12a})N$-N(H)-; one of R_{11} and R_{12} is hydrogen and the other is selected from phenylalkyl and diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is phenyl.

A more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined above and R_5 is alkylene or R_3 is R_6-S(O)$_2$-R_7- or R_{26}-S(O)-R_{27}- wherein R_7 is alkylene, R_{27} is alkylene and R_6 and R_{26} are defined as above.

Another more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$ and R_3 is R_4-C(O)-N(R_{20})-R_8- or R_6-S(O)$_2$-N(R_{21})-R_{10}- wherein R_8 and R_{10} are alkylene and R_4, R_6, R_{20} and R_{21} are defined as above.

An even more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is tetrazolyl or -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group or R is tetrazolyl or R is -C(O)-NHS(O)$_2$$R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 and R_2 are independently selected from (i) loweralkyl, (ii) cycloalkyl, (iii) substituted aryl wherein aryl is phenyl substituted with one, two or three substituents independently selected from loweralkyl, alkoxy, halo, alkoxyalkoxy and carboxyalkoxy, (iv) substituted or unsubstituted heterocyclic, (v) alkenyl, (vi) heterocyclic (alkyl), (vii) arylalkyl, (viii) aryloxyalkyl, (ix) (N-alkanoyl-N-alkyl)aminoalkyl and (x) alkylsulfonylamidoalkyl, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- wherein R_{11} and R_{12} are independently selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl, arylalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, and trialkylaminoalkyl, and R_5 is alkylene; or R_3 is R_4-C(O)-N(R_{20})-R_8- or R_6-S(O)$_2$-N(R_{21})-R_{10}- wherein R_4 is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and R_6 is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl, R_8 and R_{10} are alkylene and R_{20} and R_{21} are loweralkyl; or

R_3 is R_6-S(O)$_2$-R_7- or R_{26}-S(O)-R_{27}- wherein R_6 is loweralkyl or haloalkyl, R_7 is alkylene, R_{26} is loweralkyl and R_{27} is alkylene.

A yet more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-NHS(O)$_2$$R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is -CH$_2$-, R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl, (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) heterocyclic (alkyl), (x) arylalkyl, (xi) aryloxyalkyl, (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofurnayl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is R_4-C(O)-N(R_{20})-R_8- or R_6-S(O)$_2$-N(R_{21})-R_{10}- wherein R_8 and R_{10} are alkylene, R_{20} and R_{21} are loweralkyl, R_4 is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and R_6 is loweralkyl, haloalkyl, alkoxyalkyl, aryl or arylalkyl.

Another yet more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-NHS(O)$_2$$R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is -CH$_2$-, R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl, (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) heterocyclic (alkyl), (x) arylalkyl, (xi) aryloxyalkyl, (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl,

8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofurnayl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is R_4-C(O)-R_5- wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})$N- wherein R_{11} and R_{12} are independently selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl, arylalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, and trialkylaminoalkyl.

Another yet more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-NHS(O)$_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is -CH_2-, R_1 is (i) loweralkyl, (ii) alkenyl, (iii) heterocyclic (alkyl), (iv) aryloxyalkyl, (v) arylalkyl, (vi) aryl, (vii) (N-alkanoyl-N-alkyl)aminoalkyl, or (viii) alkylsulfonylamidoalkyl, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofurnayl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R_3 is R_4-C(O)-R_5- wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})$N- wherein R_{11} is loweralkyl and R_{12} is aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, or heterocyclic.

Another yet more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-NHS(O)$_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is -CH_2-, R_1 is (i) loweralkyl, (ii) alkenyl, (iii) heterocyclic (alkyl), (iv) aryloxyalkyl, (v) arylalkyl, (vi) (N-alkanoyl-N-alkyl)aminoalkyl, or (vii) alkylsulfonylamidoalkyl,(vii) phenyl, or (ix) substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R_3 is R_6-S(O)$_2$-N(R_{21})-R_{10}- wherein R_{10} is alkylene, R_6 is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl and R_{21} is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl.

Another yet more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group,

tetrazolyl or -C(O)-NHS$(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is -CH_2-, R_1 is (i) substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl or 1,4-benzodioxanyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy and alkoxyalkoxy, (ii) loweralkyl, (iii) alkenyl, (iv) heterocyclic (alkyl), (v) aryloxyalkyl, (vi) arylalkyl, (vii) (N-alkanoyl-N-alkyl)aminoalkyl, (viii) alkylsulfonylamidoalkyl,or (ix) phenyl, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R_3 is alkoxycarbonyl or R_6-S$(O)_2$-N(R_{21})-R_{10}- wherein R_{10} is alkylene, R_6 is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{21} is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl.

Another yet more preferred embodiment of the invention is a = compound of formula (I) or (II) wherein n is 0, R is -C$(O)_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-NHS$(O)_2R_{16}$ wherein R_{16} is loweralkyl or haloalkyl, Z is -CH_2-, R_1 is loweralkyl,alkenyl, heterocyclic (allkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl,, or alkylsulfonylamidoalkyl, and R_3 is R_4-C(O)-R_5- wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$- wherein R_{11} and R_{12} are independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

A still more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is -C$(O)_2$-G wherein G is hydrogen or a carboxy protecting group, tetrazolyl or -C(O)-NHS$(O)_2R_{16}$ wherein R_{16} is loweralkyl or haloalkyl, Z is -CH_2-, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, (ii) loweralkyl, (iii) alkenyl, (iv) heterocyclic (alkyl), (v) aryloxyalkyl, (vi) arylalkyl, (vii) (N-alkanoyl-N-alkyl)aminoalkyl, (viii) alkylsulfonylamidoalkyl,or (ix) phenyl, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is R_4-C(O)-R_5- wherein R_5 is alkylene and R_4 is

$(R_{11})(R_{12})N$- wherein R_{11} and R_{12} are independently selected from loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, or heterocyclic.

Another still more preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl or haloalkyl, Z is $-CH_2-$, R_1 is loweralkyl, alkenyl, heterocyclic (alkyl), aryloxyalkyl, arylalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, phenyl, or alkoxyalkyl, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$- wherein R_{11} and R_{12} are independently selected from loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, or heterocyclic.

A most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$- wherein R_{11} and R_{12} are independently selected from loweralkyl.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$- wherein R_{11} is loweralkyl and R_{12} is aryl.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group, Z is -CH$_2$-, R$_1$ is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, R$_2$ is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R$_3$ is R$_6$-S(O)$_2$-N(R$_{21}$)-R$_{10}$- wherein R$_{10}$ is alkylene, R$_6$ is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R$_{21}$ is loweralkyl, haloalkyl or alkoxyalkyl.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group, Z is -CH$_2$-, R$_1$ is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, R$_2$ is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R$_3$ is R$_4$-C(O)-R$_5$- wherein R$_5$ is alkylene and R$_4$ is (R$_{11}$)(R$_{12}$)N- wherein R$_{11}$ is alkyl and R$_{12}$ is selected from aryl, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, R is -C(O)$_2$-G wherein G is hydrogen or a carboxy protecting group, Z is -CH$_2$-, R$_1$ is loweralkyl,alkenyl, heterocyclic (alkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl, or alkylsulfonylamidoalkyl, and R$_3$ is R$_4$-C(O)-R$_5$- wherein R$_5$ is alkylene and R$_4$ is (R$_{11}$)(R$_{12}$)N- wherein R$_{11}$ and R$_{12}$ are independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic, with the proviso that one or R$_{11}$ and R$_{12}$ is alkyl.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined therein and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, R_1 is loweralkyl, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined therein and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, R_1 is alkenyl, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined therein and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, R_1 is heterocyclic (alkyl), and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined therein and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, R_1 is aryloxyalkyl, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined therein and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, R_1 is arylalkyl, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined therein and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, R_1 is aryl, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined therein and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, R_1 is (N-alkanoyl-N-alkyl)aminoalkyl, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined therein and R_5 is alkylene.

Another most highly preferred embodiment of the invention is a compound of formula (I) or (II) wherein n is 0, Z is $-CH_2-$, R_1 is alkylsulfonylamidoalkyl, and R_3 is R_4-C(O)-R_5- wherein R_4 is $(R_{11})(R_{12})N$- as defined therein and R_5 is alkylene.

The present invention also relates to processes for preparing the compounds of formula (I) and (II) and to the synthetic intermediates employed in these processes.

The present invention also relates to a method of antagonizing endothelin in a mammal (preferably, a human) in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of formula (I) or (II).

The invention further relates to endothelin antagonizing compositions comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of formula (I) or (II).

In another embodiment of the invention is disclosed a method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

In another embodiment of the invention is disclosed a method for preventing new bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

In another embodiment of the instant invention, therefore, is disclosed a method for inhibiting metastatic growth in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

In another embodiment of the invention is disclosed a method for inhibiting bone loss in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

In another embodiment of the instant invention, is disclosed a method for inhibiting bone turnover in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

In another embodiment of the invention is disclosed a method for the reduction of cancer related pain in a patient in need thereof which comprises administering to the patient a therapeutically effective amount of an endothelin ET-A receptor antagonist.

In another embodiment of the instant invention is disclosed therapeutically acceptable formulations of an endothelin ET-A receptor antagonist, optionally in the presence of a co-therapeutic agent, for use in these methods.

Brief Description of the Drawings

Figure 1 illustrates levels of interleukin-6 (IL-6) in a subject population treated with a placebo or 2.5 mg or 10 mg ABT-627.

Figure 2 illustrates levels of prostate specific antigen (PSA) in a subject population treated with a placebo or 2.5 mg or 10 mg of ABT-627.

Figure 3 illustrates VAS score levels relating to pain assessment in a subject population treated with a placebo or 2.5 mg or 10 mg of ABT-627.

Figure 4 illustrates crosslinked N-telopeptides (degradation) in a subject population treated with a placebo or 10 mg ABT-627.

Figure 5 illustrates bone alkaline phosphatase (BAP) formation in a subject population treated with a placebo or 10 mg ABT-627.

Figure 6 illustrates skeletal involvement in a subject population treated with a placebo or 10 mg ABT-627.

Figure 7 illustrates acid phosphatase levels in a subject population treated with a placebo or 10 mg ABT-627.

The compounds of the invention comprise two or more asymmetrically substituted carbon atoms. As a result, racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13 - 30.

The term "carboxy protecting group" as used herein refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo* , for example by enzymatic hydrolysis, to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference. Examples of esters useful as prodrugs for compounds containing

carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy protecting groups are C_1 to C_8 alkyl (e.g., methyl, ethyl or tertiary butyl and the like); haloalkyl; alkenyl; cycloalkyl and substituted derivatives thereof such as cyclohexyl, cylcopentyl and the like; cycloalkylalkyl and substituted derivatives thereof such as cyclohexylmethyl, cylcopentylmethyl and the like; arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxyl)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undersirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl,

t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a carbonyl (-C(O)-) group. Examples of alkanoyl include acetyl, propionyl and the like.

The term "alkanoylamino" as used herein refers to an alkanoyl group as previously defined appended to an amino group. Examples alkanoylamino include acetamido, propionylamido and the like.

The term "alkanoylaminoalkyl" as used herein refers to R_{43}-NH-R_{44}- wherein R_{43} is an alkanoyl group and R_{44} is an alkylene group.

The term "alkanoyloxyalkyl" as used herein refers to R_{30}-O-R_{31}- wherein R_{30} is an alkanoyl group and R_{31} is an alkylene group. Examples of alkanoyloxyalkyl include acetoxymethyl, acetoxyethyl and the like.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon radical containing from 2 to 15 carbon atoms and also containing at least one carbon-carbon double bond. Alkenyl groups include, for example, vinyl (ethenyl), allyl (propenyl), butenyl, 1-methyl-2-buten-1-yl and the like.

The term "alkenylene" denotes a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 15 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include $-CH=CH-$, $-CH_2CH=CH-$, $-C(CH_3)=CH-$, $-CH_2CH=CHCH_2-$, and the like.

The term "alkenyloxy" as used herein refers to an alkenyl group, as previously defined, connected to the parent molecular moiety through an oxygen (-O-) linkage. Examples of alkenyloxy include allyloxy, butenyloxy and the like.

The term "alkoxy" as used herein refers to $R_{41}O-$ wherein R_{41} is a loweralkyl group, as defined herein. Examples of alkoxy include, but are not limited to, ethoxy, tert-butoxy, and the like.

The term "alkoxyalkoxy" as used herein refers to $R_{80}O-R_{81}O-$ wherein R_{80} is loweralkyl as defined above and R_{81} is alkylene. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like.

The term "alkoxyalkoxyalkyl" as used herein refers to an alkoxyalkoxy group as previously defined appended to an alkyl radical. Representative examples of alkoxyalkoxyalkyl groups include methoxyethoxyethyl, methoxymethoxymethyl, and the like.

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl radical as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like.

The term "alkoxycarbonyl" as used herein refers to an alkoxyl group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like.

The term "alkoxycarbonylalkenyl" as used herein refers to an alkoxycarbonyl group as previously defined appended to an alkenyl radical. Examples of alkoxycarbonylalkenyl include methoxycarbonylethenyl, ethoxycarbonylethenyl and the like.

The term "alkoxycarbonylalkyl" as used herein refers to $R_{34}-C(O)-R_{35}-$ wherein R_{34} is an alkoxy group and R_{35} is an alkylene group. Examples of alkoxycarbonylalkyl include methoxycarbonylmethyl, methoxcarbonylethyl, ethoxycarbonylmethyl and the like.

The term "alkoxycarbonylaminoalkyl" as used herein refers to $R_{38}-C(O)-NH-R_{39}-$ wherein R_{38} is an alkoxy group and R_{39} is an alkylene group.

The term "alkoxycarbonyloxyalkyl" as used herein refers to $R_{36}-C(O)-O-R_{37}-$ wherein R_{36} is an alkoxy group and R_{37} is an alkylene group.

The term "(alkoxycarbonyl)thioalkoxy" as used herein refers to an alkoxycarbonyl group as previously defined appended to a thioalkoxy radical. Examples of (alkoxycarbonyl)thioalkoxy include methoxycarbonylthiomethoxy, ethoxycarbonylthiomethoxy and the like.

The term "alkoxyhaloalkyl" as used herein refers to a haloalkyl radical to which is appended an alkoxy group.

The terms "alkyl" and "loweralkyl" as used herein refer to straight or branched chain alkyl radicals containing from 1 to 15 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "(N-alkanoyl-N-alkyl)aminoalkyl" as used herein refers to $R_{85}C(O)N(R_{86})R_{87}$- wherein R_{85} is an alkanoyl as previously defined, R_{86} is loweralkyl, and R_{87} is alkylene.

The term "alkylamino" as used herein refers to $R_{51}NH$- wherein R_{51} is a loweralkyl group, for example, ethylamino, butylamino, and the like.

The term "alkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylamino group.

The term "alkylaminocarbonyl" as used herein refers to an alkylamino group, as previously defined, appended to the parent molecular moiety through a carbonyl (-C(O)-) linkage. Examples of alkylaminocarbonyl include methylaminocarbonyl, ethylaminocarbonyl, isopropylaminocarbonyl and the like.

The term "alkylaminocarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended an alkylaminocarbonyl group.

The term "alkylaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylaminocarbonyl group.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to R_{40}-C(O)-NH-R_{41}- wherein R_{40} is an alkylamino group and R_{41} is an alkylene group.

The term "alkylene" denotes a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 15 carbon atoms by the removal of two hydrogen atoms, for example $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$ and the like.

The term "alkylsulfonylamidoalkyl" as used herein refers $R_{88}S(O)_2NHR_{89}$- wherein R_{88} is loweralkyl and R_{89} is alkylene.

The term "alkylsulfonylamino" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a sulfonylamino ($-S(O)_2-NH-$) group. Examples of alkylsulfonylamino include methylsulfonylamino, ethylsulfonylamino, isopropylsulfonylamino and the like.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon radical containing from 2 to 15 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include -C≡C-H, H-C≡C-CH_2-, H-C≡C-$CH(CH_3)$- and the like.

The term "alkynylene" refers to a divalent group derived by the removal of two hydrogen atoms from a straight or branched chain acyclic hydrocarbon group containing from 2 to 15 carbon atoms and also containing a carbon-carbon triple bond. Examples of alkynylene include -C≡C-, -C≡C-CH_2-, -C≡C-CH(CH_3)- and the like.

The term "aminoalkyl" as used herein refers to a -NH_2, alkylamino, or dialkylamino group appended to the parent molecular moiety through an alkylene.

The term "aminocarbonyl" as used herein refers to H_2N-C(O)- .

The term "aminocarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended an aminocarbonyl (NH_2C(O)-) group.

The term "aminocarbonylalkoxy" as used herein refers to H_2N-C(O)- appended to an alkoxy group as previously defined. Examples of aminocarbonylalkoxy include aminocarbonylmethoxy, aminocarbonylethoxy and the like.

The term "aminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an aminocarbonyl (NH_2C(O)-) group.

The term "trialkylaminoalkyl" as used herein refers to (R_{90})(R_{91})(R_{92})N(R_{93})- wherein R_{90}, R_{91}, and R_{92} are independently selected from loweralkyl and R_{93} is alkylene.

The term "aroyloxyalkyl" as used herein refers to R_{32}-C(O)-O-R_{33}- wherein R_{32} is an aryl group and R_{33} is an alkylene group. Examples of aroyloxyalkyl include benzoyloxymethyl, benzoyloxyethyl and the like.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, halo, haloalkyl, haloalkoxy, hydroxyalkyl, alkenyloxy, alkoxy, alkoxyalkoxy, alkoxycarbonyl, alkoxycarbonylalkenyl, (alkoxycarbonyl)thioalkoxy, thioalkoxy, amino, alkylamino, dialkylamino, aminoalkyl, trialkylaminoalkyl, aminocarbonyl, aminocarbonylalkoxy, alkanoylamino, arylalkoxy, aryloxy, mercapto, cyano, nitro, carboxaldehyde, carboxy, carboxyalkenyl, carboxyalkoxy, alkylsulfonylamino, cyanoalkoxy, (heterocyclic)alkoxy, hydroxy, hydroxalkoxy, phenyl and tetrazolylalkoxy. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group, for example, phenylethenyl and the like.

The term "arylalkoxy" as used herein refers to R_{42}O- wherein R_{42} is an arylalkyl group, for example, benzyloxy, and the like.

The term "arylalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group, for example, benzyloxymethyl and the like.

The term "arylalkyl" as used herein refers to an aryl group as previously defined, appended to a loweralkyl radical, for example, benzyl, phenethyl, 2,2-dimethyl-1-phenyl-1-propyl, 3,3-dimethyl-1-phenyl-1-butyl, and the like.

The term "aryloxy" as used herein refers to $R_{45}O$- wherein R_{45} is an aryl group, for example, phenoxy, and the like.

The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkylcarbonyloxy group (i.e., $R_{62}C(O)O$- wherein R_{62} is an arylalkyl group).

The term "aryloxyalkyl" refers to an aryloxy group as previously defined appended to an alkyl radical. Examples of aryloxyalkyl include phenoxymethyl, 2-phenoxyethyl and the like.

The term "carboxaldehyde" as used herein refers to a formaldehyde radical, -C(O)H.

The term "carboxy" as used herein refers to a carboxylic acid radical, -C(O)OH.

The term "carboxyalkenyl" as used herein refers to a carboxy group as previously defined appended to an alkenyl radical as previously defined. Examples of carboxyalkenyl include 2-carboxyethenyl, 3-carboxy-1-ethenyl and the like.

The term "carboxyalkoxy" as used herein refers to a carboxy group as previously defined appended to an alkoxy radical as previously defined. Examples of carboxyalkoxy include carboxymethoxy, carboxyethoxy and the like.

The term "cyanoalkoxy" as used herein refers to an alkoxy radical as previously defined to which is appended a cyano (-CN) group. Examples of cyanoalkoxy include 3-cyanopropoxy, 4-cyanobutoxy and the like.

The term "cycloalkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyloxy group (i.e., R_{60}-C(O)-O- wherein R_{60} is a cycloalkyl group).

The term "cycloalkyl" as used herein refers to an aliphatic ring system having 3 to 10 carbon atoms and 1 to 3 rings including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl, and the like. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "dialkylamino" as used herein refers to $R_{56}R_{57}N$- wherein R_{56} and R_{57} are independently selected from loweralkyl, for example diethylamino, methyl propylamino, and the like.

The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group.

The term "dialkylaminocarbonyl" as used herein refers to a dialkylamino group, as previously defined, appended to the parent molecular moiety through a carbonyl (-C(O)-) linkage. Examples of dialkylaminocarbonyl include dimethylaminocarbonyl, diethylaminocarbonyl and the like.

The term "dialkylaminocarbonylalkenyl" as used herein refers to an alkenyl radical to which is appended a dialkylaminocarbonyl group.

The term "dialkylaminocarbonylalkyl" as used herein refers to R_{50}-C(O)-R_{51}- wherein R_{50} is a dialkylamino group and R_{51} is an alkylene group.

The term “diarylalkyl,” as used herein, refers to two aryl groups, as defined herein, attached to the parent molecular moiety through an alkyl group. The aryl groups of the diaryl can be optionally substituted with 1-5 alkyl substituents. Examples of “diaryl” include diphenylmethyl (benzhydryl), 2,2-diphenylethyl, 1,2-diphenylethyl, bis(2-methylphenyl)methyl, and the like.

The term "halo" or "halogen" as used herein refers to I, Br, Cl or F.

The term "haloalkenyl" as used herein refers to an alkenyl radical to which is appended at least one halogen substituent.

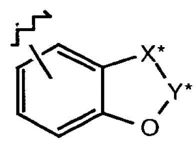
The term "haloalkoxy" as used herein refers to an alkoxy radical as defined above, bearing at least one halogen substituent, for example, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, trifluoromethoxy, 2,2,3,3,3-pentafluoropropoxy and the like.

The term "haloalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended a haloalkoxy group.

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, to which is appended at least one halogen substituent, for example, chloromethyl, fluoroethyl, trifluoromethyl or pentafluoroethyl and the like.

The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; or two sulfur atoms in non-adjacent positions. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The nitrogen heteroatoms can be optionally quaternized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or a cyclohexane ring or another heterocyclic ring (for example, indolyl, dihydroindolyl, quinolyl,

isoquinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, decahydroisoquinolyl, benzofuryl, dihydrobenzofuryl or benzothienyl and the like). Heterocyclics include: aziridinyl, azetidinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, oxetanyl, furyl, tetrahydrofuranyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, pyrimidyl and benzothienyl.

Heterocyclics also include compounds of the formula  where X* is $-CH_2-$ or -O- and Y* is -C(O)- or $[-C(R'')_2-]_v$ where R" is hydrogen or C_1-C_4-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like. Heterocyclics also include bicyclic rings such as quinuclidinyl and the like.

Heterocyclics can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, aminoalkyl, trialkylaminoalkyl, haloalkyl, cycloalkyl, aryl, arylalkyl, -COOH, $-SO_3H$, alkoxycarbonyl, nitro, cyano and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "(heterocyclic)alkoxy" as used herein refers to a heterocyclic group as defined above appended to an alkoxy radical as defined above. Examples of (heterocyclic)alkoxy include 4-pyridylmethoxy, 2-pyridylmethoxy and the like.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above.

The term "heterocycliccarbonyloxyalkyl" as used herein refers to R_{46}-C(O)-O-R_{47}- wherein R_{46} is a heterocyclic group and R_{47} is an alkylene group.

The term "hydroxy" as used herein refers to -OH.

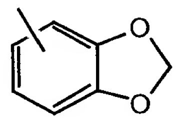
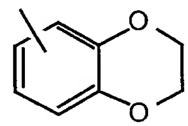
The term "hydroxyalkenyl" as used herein refers to an alkenyl radical to which is appended a hydroxy group.

The term "hydroxyalkoxy" as used herein refers to an alkoxy radical as previously defined to which is appended a hydroxy (-OH) group. Examples of hydroxyalkoxy include 3-hydroxypropoxy, 4-hydroxybutoxy and the like.

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is appended a hydroxy group.

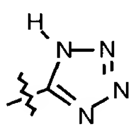
The term "leaving group" as used herein refers to a halide (for example, Cl, Br or I) or a sulfonate (for example, mesylate, tosylate, triflate and the like).

The term "mercapto" as used herein refers to -SH.

The terms "methylenedioxy" and "ethylenedioxy" refer to one or two carbon chains attached to the parent molecular moiety through two oxygen atoms. In the case of methylenedioxy, a fused 5 membered ring is formed. In the case of ethylenedioxy, a fused 6 membered ring is formed. Methylenedixoy substituted on a phenyl ring results in the formation of a benzodioxolyl radical.  . Ethylenedioxy substituted on a phenyl ring results in the formation of a benzodioxanyl radical  .

The term "substantially pure" as used herein means 95% or more of the specified compound.

The term "tetrazolyl" as used herein refers to a radical of the formula

 or a tautomer thereof.

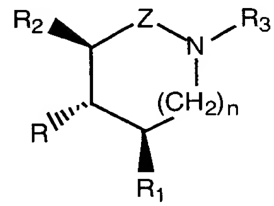
The term "tetrazolylalkoxy" as used herein refers to a tetrazolyl radical as defined above appended to an alkoxy group as defined above. Examples of tetrazolylalkoxy include tetrazolylmethoxy, tetrazolylethoxy and the like.

The term "thioalkoxy" as used herein refers to $R_{70}S$- wherein R_{70} is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like.

The term "thioalkoxyalkoxy" as used herein refers to $R_{80}S$-$R_{81}O$- wherein R_{80} is loweralkyl as defined above and R_{81} is alkylene. Representative examples of alkoxyalkoxy groups include CH_3SCH_2O-, $EtSCH_2O$-, t-$BuSCH_2O$- and the like.

The term "thioalkoxyalkoxyalkyl" as used herein refers to a thioalkoxyalkoxy group appended to an alkyl radical. Representative examples of alkoxyalkoxyalkyl groups include $CH_3SCH_2CH_2OCH_2CH_2$-, $CH_3SCH_2OCH_2$-, and the like.

The term *"trans,trans"* as used herein refers to the orientation of substituents (R_1 and R_2) relative to the central substituent R as shown



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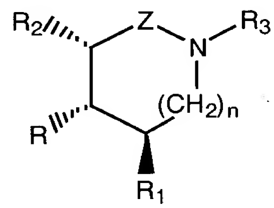
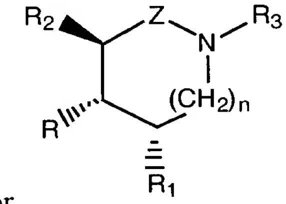
The term *"trans,cis"* as used herein refers to the orientation of substituents (R_1 and R_2) relative to the central substituent R as shown



or



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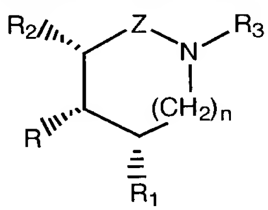
This definition encompasses both the case where R and R_2 are *cis* and R and R_1 are *trans* and the case where R_2 and R are *trans* and R and R_1 are *cis.*

The term *"cis,cis"* as used herein refers to the orientation of substituents (R_1 and R_2) relative to the central substituent R as shown



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Preferred compounds of the invention are selected from the group consisting of:

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[3-(N-propyl-N-*n*-pentanesulfonylamino)propyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-Methoxymethoxyphenyl)-4-(1,3-benzodioxol-5-yl)--(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(3,4-Dimethoxyphenyl)-4-(1,3-benzodioxol -5-yl)-1-[2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(3,4-Dimethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-*n*-hexanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(3,4-Difluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(3,4-Difluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-*n*-hexanesulfonylamino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(3-chloropropanesulfonyl)amino)ethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(3-chloropropanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(4-methylbutanesulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-Methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(*n*-pentanesulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(2,2,3,3,3-pentafluoropropoxyethanesulfonyl)-amino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(1,4-Benzodioxan-6-yl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(*n*-pentanesulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(3-chloropropanesulfonyl)amino)-ethyl)pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(pentanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-((2,2,2-trifluoroethoxyethane)sulfonyl)amino)-ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(butanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(2-methylpropanesulfonyl)amino)ethyl]pyrrolidine-3-carboxylic acid;

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(butanesulfonylamino))ethyl)pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-Methylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-Dioxo-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Tetrahydro-2*H*-pyran)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,4-Trimethyl-3-pentenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-Dioxo-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[[*N*-4-heptyl-*N*(2 methyl-3-fluorophenyl)] amino carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-dimethylpentyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Methoxyphenyl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethyl-3-(*E*)-pentenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S, 3R, 4S)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(*2S, 3R, 4S*)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

(2R,3R,4S)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)1-(2-(N-propyl-N-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylamino)butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylamino)butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylamino)butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylamino)butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,4-Trimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,4-Trimethylpent-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylamino)butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,4-Trimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,4-Trimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,4-Trimethylpent-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylamino)butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,-Dimethyl-2-(1,3-Dioxol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,-Dimethyl-2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Methoxyphenyl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Methoxyphenyl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Methoxyphenyl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1- (N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Methoxyphenyl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Methoxyphenyl)-ethyl)-4-(7-methcxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-((2-Methoxyphenoxy)-methyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1- (N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-((2-Methoxyphenoxy)-methyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Methoxyphenoxy)-methyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxo 1,2-dihydro pyridin-1-yl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyridin-1-yl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyridin-1-yl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyridin-1-yl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(N-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyridin-1-yl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyridin-1-yl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2(-2-Oxopiperidin-1-yl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(N-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopiperidin-1-yl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopiperidin-1-yl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(N-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopiperidin-1-yl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(N-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopiperidin-1-yl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopiperidin-1-yl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(propoxy)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4 dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-trimethylammoniobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(N-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(propoxy)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-trimethylammoniobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-(N,N-di(N-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(3,3-Dimethyl-2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(N-butyl)aminocarbonylmethyl)-yrrolidine-3-carboxylic acid;

trans,trans-2-(2-(3,3-Dimethyl-2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(3,3-Dimethyl-2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(4,4-Dimethyl-2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(N-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(4,4-Dimethyl-2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(4,4-Dimethyl-2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-dibutylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(propoxy)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4 dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-propanesultamyl)ethyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N-butyl-N-(propoxy)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-dibutylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-(N,N-dibutylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-oxazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Oxazol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Oxazol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Oxazol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(propoxy)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Oxazol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Oxazol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Oxazol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Oxazol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(5-Methyloxazol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(5-Methyloxazol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(5-Methyloxazol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2,5-Dioxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2,5-Dioxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2,5-Dioxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2,5-Dioxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(propoxy)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2,5-Dioxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl) amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2,5-Dioxopyrrolidin-1-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2,5-Dioxopyrrolidin-1-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyridin-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyridin-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(3-hydroxypropyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyridin-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(propoxy)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyridin-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyridin-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyridin-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyridin-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyrimidin-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyrimidin-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(Pyrimidin-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-benzodioxol-4-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-benzodioxol-4-yl)ethyl)-4-(1,3-benzodioxol- 5-yl)-1-[(N-4-heptyl-N-(4-fluoro-3-methylphenyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid; and

trans,trans-2-(2-(1,3-benzodioxol-4-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[(N-butyl-N-(4 dimethylaminobutyl)amino)carbonylmethyl]-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-(2,2-Dimethylpent-(E)-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-(2,2-Dimethylpent-(E)-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-(2-(2-Methoxyphenyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

or a pharmaceutically acceptable salt.

Most preferred compounds of the invention are selected from the group consisting of:

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-[[N-4-heptyl-N-(2-methyl-3-fluorophenyl)] aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2,-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-Methoxyphenyl)-ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2,2-Dimethyl-3-(E)-pentenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S, 3R, 4S)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S, 3R, 4S)-2-(2,2 Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S, 3R, 4S)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2R, 3R, 4S)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[((N-propyl-N-pentanesulfonyl)amino)ethyl]-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-(2,2-Dimethylpent-(E)-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-(2,2-Dimethylpent-(E)-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

(2S,3R,4S)-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid; and

(2S,3R,4S)-2-(2-(2-Methoxyphenyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-(pyrrolidine-3-carboxylic acid;

trans,trans-2-[4-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-[4-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-[4-(2-isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(3,3-dimethyl-1-phenylbutyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-[4-(2-isopropopoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-((1-(o-tolyl)-1-(o-ethylphenyl)-methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;

trans,trans-2-(4-(2-(2-propoxy)ethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1- N-phenyl-N-t-butylhydrazino carbonylmethyl)-pyrrolidine-3-carboxylic acid; and

trans,trans-2-(4-(2-methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-phenyl-N-t-butylhydrazino carbonylmethyl)-pyrrolidine-3-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

Methods for preparing the compounds of the invention are shown in Schemes I-XXIII.

Scheme I illustrates the general procedure for preparing the compounds of the invention when n and m are 0, Z is $-CH_2-$ and W is $-CO_2H$. A alpha-ketoester 1, where E is loweralkyl or a carboxy protecting group is reacted with a nitro vinyl compound 2, in the presence of a base (for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or sodium ethoxide or sodium hydride and the like) in an inert solvent such as toluene, benzene, tetrahydrofuran or ethanol and the like. The condensation product 3 is reduced (for example, hydrogenation using a Raney nickel or platinum catalyst). The resulting amine cyclizes to give the dihydro pyrrole 4. Reduction of 4 (for example, sodium cyanoborohydride or catalytic hydrogenation and the like) in a protic solvent such as ethanol or methanol and the like gives the pyrrolidine compound 5 as a mixture of *cis-cis*, *trans,trans* and *cis,trans* products. Chromatographic separation removes the *cis-cis* isomer leaving a mixture of the *trans,trans* and *cis,trans* isomers which is further elaborated. The *cis-cis* isomer can be epimerized (for example, using sodium ethoxide in ethanol) to give the *trans,trans* isomer and then carried on as described below. The pyrrolidine nitrogen is (1) acylated or sulfonylated with R_3-X (R_3 is R_4-C(O)- or R_6-$S(O)_2$- and X is a leaving group such as a halide (Cl is preferred) or X taken together with R_4-C(O)- or R_6-$S(O)_2$- forms an activated ester including esters or anhydrides derived from formic acid, acetic acid and the like, alkoxycarbonyl halides, N-hydroxysuccinimide, N-hydroxyphthalimide, N-hydroxybenzotriazole, N-hydroxy-5-norbornene-2,3-dicarboxamide, 2,4,5-trichlorophenol and the like) or (2) alkylated with R_3-X where X is a leaving group (for example, X is a halide (for example, Cl, Br or I) or X is a leaving group such as a sulfonate (for example, mesylate, tosylate, triflate and the like)) in the presence of a base such as diisopropyl ethylamine or triethylamine and the like to give the N-derivatized pyrrolidine 6 which is still a mixture of *trans,trans* and *cis,trans* isomers. Hydrolysis of the ester 6 (for example, using a base such a sodium hydroxide in $EtOH/H_2O$) selectively hydrolyzes the *trans,trans* ester to give a mixture of 7 and 8, which are readily separated.

Scheme II illustrates a general procedure for preparing the compounds of the invention when n is 1, m is 0, Z is $-CH_2-$ and W is $-CO_2H$. A substituted benzyl chloride 9 is reacted with a lithio dithiane 10 in an inert solvent such as THF or dimethoxyethane to give the alkylated adduct 11. The anion of compound 11 is formed using a base such as n-butyllithium and then reacted with R_1-CH_2-X' wherein X' is a leaving group such as a halide or sulfonate to give compound 12. The dithiane protecting group is cleaved (for example, using a mercuric salt in water) to give the keto compound 13. Reaction of ketone 13 with benzyl amine and formaldehyde gives the keto piperidine compound 14. Treatment of compound 14 with an activated nitrile such as trimethylsilyl cyanide followed by a dehydrating agent such as phosphorous oxychloride provides the isomeric ene nitriles 15. Reduction of the double

bond (for example, using sodium borohydride) affords the piperidinyl nitrile 16. Hydrolysis of the nitrile using hydrochloric acid in the presence of a carboxy protecting reagent (for example, an alkyl alcohol) affords ester 17 (where E is a carboxy protecting group). Debenzylation by catalytic hydrogenation under acidic conditions affords the free piperidine compound 18. Compound 18 is further elaborated by the procedures described in Scheme I for compound 5 to give the final product compound 19.

Scheme III illustrates a general procedure for preparing the compounds of the invention when m and n are 0, Z is -C(O)- and W is $-CO_2H$. alpha-Keto ester 20 (wherein E is loweralkyl or a carboxy protecting group) is reacted with an alpha-haloester 21 (where J is lower alkyl or a carboxy protecting group and the halogen is bromine, iodine or chlorine) in the presence of a base such as NaH or potassium tert-butoxide or lithium diisopropylamide in an inert solvent such as THF or dimethoxyethane to give diester 22. Treating compound 22 with R_3-NH_2 and heating in acetic acid gives the cyclic compound 23. The double bond is reduced (for example, by catalytic hydrogenation using a palladium on carbon catalyst or sodium cyanoborohydride reduction) to give pyrrolidone 24. Epimerization with sodium ethoxide in ethanol to give the desired *trans,trans* configuration, followed by sodium hydroxide hydrolysis of the ester, affords the desired *trans,trans* carboxylic acid 25.

Scheme IV illustrates a general procedure for preparing the compounds of the invention when n is 0, m is 1, Z is $-CH_2-$ and W is $-CO_2H$. The *trans,trans* compound 7, prepared in Scheme I, is homologated by the Arndt-Eistert synthesis. The carboxy terminus is activated (for example, by making the acid chloride using thionyl chloride) to give compound 52, where L is a leaving group (in the case of an acid chloride, L is Cl). Compound 52 is treated with diazomethane to give the diazo ketone 53. Rearrangement of compound 53 (for example, using water or an alcohol and silver oxide or silver benzoate and triethylamine, or heating or photolysis in the presence of water or an alcohol) affords the acetic acid compound 54 or an ester which may be hydrolyzed. Compounds where m is from 2 to 6 can be obtained by repetition of the above described process.

A preferred embodiment is shown in Schemes V and VI. A benzoyl acetate 26 is reacted with a nitro vinyl benzodioxolyl compound 27 using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base in toluene to give compound 28. Catalytic hydrogenation using Raney nickel leads to reduction of the nitro group to an amine and subsequent cyclization to give the dihydropyrrole 29. The double bond is reduced with sodium cyanoborohydride to give the pyrrolidine compound 30 as a mixture of *cis-cis*, *trans,trans* and *cis,trans* isomers. Chromatography separates out the *cis-cis* isomer, leaving a mixture of the *trans,trans* and *cis,trans* isomers (31).

Scheme VI illustrates the further elaboration of the *trans,trans* isomer. The mixture (31) of *trans,trans* and *cis,trans* pyrrolidines described in Scheme IV is reacted with N-propyl

bromoacetamide in acetonitrile in the presence of ethyldiisopropylamine to give the alkylated pyrrolidine compound 32, still as a mixture of *trans,trans* and *cis,trans* isomers. Sodium hydroxide in ethanol-water hydrolyzes the ethyl ester of the *trans,trans* compound but leaves the ethyl ester of the cis,trans compound untouched, thus allowing separation of the *trans,trans* carboxylic acid 33 from the *cis,trans* ester 34.

Scheme VII illustrates the preparation of a specific piperidinyl compound. Benzodioxolyl methyl chloride 35 is reacted with lithio dithiane 36 to give the alkylated compound 37. Treatment of compound 37 with 4-methoxybenzyl chloride in the presence of lithium diisopropylamide gives compound 38. Cleavage of the dithiane protecting group using a mercuric salt in aqueous solution gives ketone 39. Treatment of 39 with benzylamine and formaldehyde gives the keto piperidine 40. Treatment of compound 40 with trimethylsilyl cyanide followed by phosphorous oxychloride gives the ene nitrile as a mixture of isomers 41. Sodium borohydride reduction of the double bond gives the piperidinyl nitrile 42. Hydrochloric acid hydrolysis in the presence of ethanol gives ethyl ester 43. The N-benzyl protecting group is removed by catalytic hydrogenation to give the free piperidine compound 44. Compound 44 is further elaborated by the procedures described in Scheme V for compound 31 resulting in the formation of the N-derivatized carboxylic acid 45.

A preferred embodiment of the process shown in Scheme III is shown in Scheme VIII. 4-Methoxybenzoylacetate 46 (wherein E is loweralkyl or a carboxy protecting group) is reacted with an benzodioxolyl alpha-bromoacetate 47 (wherein E is lower alkyl or a carboxy protecting group) in the presence of NaH in THF to give diester 48. Treating compound 48 with ethoxypropylamine and heating in acetic acid gives the cyclic compound 49. The double bond is reduced by catalytic hydrogenation using a palladium on carbon catalyst to give pyrrolidone 50. Epimerization with sodium ethoxide in ethanol to give the desired *trans,trans* configuration is followed by sodium hydroxide hydrolysis of the ester to afford the desired *trans,trans* carboxylic acid 51.

Scheme IX illustrates the preparation of compounds where n is 0, Z is -CH_2-, and W is other than carboxylic acid. Compound 55, which can be prepared by the procedures described in Scheme IV, is converted (for example, using peptide coupling condition, e.g. N-methylmorpholine, EDCI and HOBt, in the presence of ammonia or other amide forming reactions) to give carboxamide 56. The carboxamide is dehydrated (for example, using phosphorus oxychloride in pyridine) to give nitrile 57. Nitrile 57 under standard tetrazole forming conditions (sodium azide and triethylamine hydrochloride or trimethylsilylazide and tin oxide) is reacted to give tetrazole 58. Alternatively nitrile 57 is reacted with hydroxylamine hydrochloride in the presence of a base (for example, potassium carbonate, sodium carbonate, sodium hydroxide, triethylamine, sodium methoxide or NaH) in a solvent such as DMF, DMSO, or dimethylacetamide to give amidoxime 59. The amidoxime 59 is

allowed to react with a methyl or ethyl chloroformate in a conventional organic solvent (such as, chloroform, methylene chloride, dioxane, THF, acetonitrile or pyridine) in the presence of a base (for example, triethylamine, pyridine, potassium carbonate and sodium carbonate) to give an O-acyl compound. Heating of the O-acyl amidoxime in an inert solvent (such as benzene, toluene, xylene, dioxane, THF, dichloroethane, or chloroform and the like) results in cyclization to compound 60. Alternatively reacting the amidoxime 59 with thionyl chloride in an inert solvent (for example, chloroform, dichloromethane, dixoane and THF and the like) affords the oxathiadiazole 61.

Scheme X illustrates the preparation of compounds in which R_3 is an acylmethylene group. A carboxylic acid 62 (where R_4 is as previously defined herein) is treated with oxalyl chloride in a solution of methylene chloride containing a catalytic amount of N,N-dimethylformamide to give the acid chloride. Treatment of the acid chloride with excess ethereal diazomethane affords a diazoketone, and then treatment with anhydrous HCl in dioxane gives the alpha-chloroketone 63. Pyrrolidine ester 5 where E is lower alkyl or a carboxy protecting group, prepared in Scheme I, is alkylated with the alpha-chloroketone 63 to provide alkylated pyrrolidine 64. Carboxy deprotection (for example, hydrolysis of an alkyl ester using lithium or sodium hydroxide in ethanol-water) gives the alkylated pyrrolidine acid 65.

Scheme XI illustrates the preparation of "reverse amides and sulfonamides". The carboxy protected pyrrolidine 5, prepared in Scheme I, is reacted with a difunctionalized compound X-R_8-X where R_8 is alkylene and X is a leaving group (for example a halide where Br is preferred) to give N-alkylated compound 66. Treatment of 66 with an amine ($R_{20}NH_2$) affords secondary amine 67. This amine (67) can be reacted with an activated acyl compound (for example, R_4-C(O)-Cl) and then carboxy deprotected (for example, hydrolysis of an ester or hydrogenation of a benzyl moiety) to afford amide 68. Alternatively amine 67 can be reacted with an activated sulfonyl compound (for example, R_6-S(O)$_2$-Cl) and then carboxy deprotected (for example, hydrolysis of an ester or hydrogenation of a benzyl moiety) to afford sulfonamide 69.

Scheme XII illustrates a method for synthesizing pyrrolidines by an azomethine ylide type [3+2]-cycloaddition to an acrylate. General structures such as compound 70 are known to add to unsaturated esters such as 71 to provide pyrrolidines such as compound 72 (O. Tsuge, S. Kanemasa, K. Matsuda, Chem. Lett. 1131-4 (1983), O. Tsuge, S. Kanemasa, T. Yamada, K. Matsuda, J. Org. Chem. 52 2523-30 (1987), and S. Kanemasa, K. Skamoto, O. Tsuge, Bull. Chem. Soc. Jpn. 62 1960-68 (1989)). A specific example is also shown in Scheme XII. Silylimine 73 is reacted with acrylate 74 in the presence of trimethylsilyl triflate and tetrabutylammonium fluoride to give the desired pyrrolidine 75 as a mixture of isomers. This method can be modified to provide the N-acetamido derivatives directly by reacting 73

and 74 with the appropriate bromoacetamide (for example, dibutyl bromoacetamide) in the presence of tetrabutylammonium iodide and cesium fluoride to give compound 76.

Scheme XIII illustrates a method for producing an enantiomerically pure pyrrolidine 80, which can be further elaborated on the pyrrolidine nitrogen. Intermediate racemic pyrrolidine ester 77 (for example, prepared by the procedure described in Scheme V) is Boc-nitrogen protected (for example, by treatment with Boc_2O) and then the ester is hydrolyzed (for example, using sodium or lithium hydroxide in ethanol and water) to give t-butyl carbamoyl pyrrolidine carboxylic acid 78. The carboxylic acid is converted to its (+)-cinchonine salt, which can be recrystallized (for example from ethyl acetate and hexane or chloroform and hexane) to afford the diastereomerically pure salt. This diastereomerically pure salt can be neutralized (for example, with sodium carbonate or citric acid) to afford enantiomerically pure carboxylic acid 79. The pyrrolidine nitrogen can be deprotected (for example, using trifluoroacetic acid) and the ester reformed by the use of ethanolic hydrochloric acid to give salt 80. Alternatively one can use ethanol HCl to cleave the protecting group and form the ester in one step. The pyrrolidine nitrogen can be further elaborated (for example, by treatment with the dibutyl amide of bromoacetamide in acetonitrile in the presence of diisopropylethylamine) to give optically active compound 81. The use of (-)-cinchonine will give the opposite enantiomer.

Scheme XIV describes another procedure for preparation of pyrrolidines. Pyrrolidines may be synthesized by the use of an azomethine ylide cycloaddition to an acrylate derivative as described by Cottrell, I. F., et.al., J. Chem. Soc., Perkin Trans. 1, 5: 1091-97 (1991). Thus, the azomethine ylide precursor 82 (where R_{55} is hydrogen or methyl) is condensed with a substituted acrylate 83 (wherein R_2 is as described herein and R_{56} is loweralkyl) under acidic conditions to afford the substituted pyrrolidine 84. The N-protecting group can be removed (for example, by hydrogenolysis of an N-benzyl group) to give 85, which can be alkylated under the conditions described above to provide the N-substituted pyrrolidine 86. Standard ester hydrolysis of 86 produces the desired pyrrolidine carboxylic acid 87.

A preferred process is shown in Scheme XV. Nitro vinyl compound (88) is reacted with beta-keto ester 89 in the presence of a base such as sodium ethoxide and the like or a trialkylamine such as triethylamine or diisopropylethylamine and the like or an amidine such as DBU and the like in an inert solvent such as THF, toluene, DMF, acetonitrile, ethyl acetate, isopropyl acetate or methylene chloride and the like at a temperature of from about 0° C to about 100° C for a period of time from about 15 minutes to overnight to give compound 90. Reduction of the nitro group followed by cyclization was effected for example by catalytic hydrogenation with a hydrogen pressure of from about atmospheric pressure to 300 p.s.i. over from about 1 hour to about 1 day of compound 90 in an inert solvent such as THF, ethyl acetate, toluene, ethanol, isopropanol, DMF or acetonitrile and the like, using a hydrogenation

catalyst such as Raney nickel, palladium on carbon, a platinum catalyst, such as platinum oxide, platinum on carbon or platinum on alumina and the like, or a rhodium catalyst, such as rhodium on carbon or rhodium on alumina and the like, and the like affords intermediate nitrone 91a or a mixture of nitrone 91a and imine 91b. The reaction mixture comprising the nitrone or nitrone/imine mixture is treated with an acid such as trifluoroacetic acid or acetic acid or sulfuric acid or phosphoric acid or methanesulfonic acid and the like, and the hydrogenation is continued to give pyrrolidine compound 92 as the *cis,cis*-isomer. Epimerization at C-3 is effected by treatment of compound 92 with a base such as sodium ethoxide, potassium t-butoxide, lithium t-butoxide or potassium t-amyloxide and the like or a trialkylamine such as triethylamine or diisopropylethylamine and the like or an amidine such as DBU and the like in an inert solvent such as ethanol, ethyl acetate, isopropyl acetate, THF, toluene or DMF and the like at a temperature of from about -20° C to about 120° C to give the *trans,trans* compound 93. Compound 93 itself can optionally be resolved into enantiomers prior to reacting with X-R_3. The substantially pure (i.e., at least 95% of the desired isomer) optically active (+)-isomer of compound 93 is obtained by treatment of a mixture of the (+)-isomer and the (-)-isomer of 93 with S-(+)-mandelic acid, D-tartaric acid or D-dibenzoyl tartaric acid and the like in a solvent such as acetonitrile, ethyl acetate, isopropyl acetate, ethanol or isopropanol and the like. The (+)-isomer of 93 selectively crystallizes as the salt, leaving the (-)-isomer of 93 in solution. Alternatively, the substantially pure (i.e., at least 95% of the desired isomer) optically active (-)-isomer of compound 93 can be selectively crystallized by reaction of a mixture of the (+)-isomer and the (-)-isomer of 93 with L-tartaric acid, L-dibenzoyl tartaric acid or L-pyroglutamic acid and the like, leaving the desired (+)-isomer of compound 93 in solution.

Compound 93 (racemic or optically active) is reacted with X-R_3 (where X is a leaving group (for example, a halide or a sulfonate) and R_3 is as previously defined) using a base such as diisopropylethylamine, triethylamine, sodium bicarbonate or potassium carbonate and the like in an inert solvent such as acetonitrile, THF, toluene, DMF or ethanol and the like at a temperature of from about 0° C to about 100° C to give the intermediate ester 94. The ester can be isolated or converted *in situ* to the carboxylic acid (95) using hydrolysis conditions such as a base such as sodium hydroxide or lithium hydroxide or potassium hydroxide and the like in a solvent such as ethanol-water or THF-ethanol and the like.

A more detailed description of the preparation of some specific analogs is provided in Schemes XVI-XXI. Aliphatic alpha-ketoesters (Scheme XVI) may be prepared by copper-catalyzed addition of a Grignard reagent (for example, propylmagnesium bromide) to an unsaturated ester, for example, ethyl 3,3-dimethylacrylate. The resultant ester is hydrolyzed, for example with sodium hydroxide in aqueous alcohol, and is homologated in stepwise fashion to the corresponding alpha-ketoester, for example by activation using

carbonyldiimidazole and condensation with magnesio-ethoxymalonate. Alternatively, olefinic alpha-ketoesters may be prepared by Claisen rearangement of the corresponding allylic alcohols; hydrolysis and homologation as described above produce the desired alpha-ketoester.

N-alkyl,O-alkyl bromohydroxamates are prepared according to Scheme XVII. N-Boc-O-allyl hydroxylamine is alkylated with and alkyl halide, for example using sodium hydride as base; the double bond is selectively reduced, for example using hydrogen and a palladium catalyst. After removal of the Boc protecting group, for example with TFA, the resultant amine is acylated, for example using bromoacetyl bromide.

The alpha-ketoesters described in Scheme XVI may be converted to pyrrolidine derivatives as described in Scheme XVIII. Michael addition onto a nitrostyrene derivative can be catalyzed with base, for example DBU or potassium t-butoxide; the resultant adduct is hydrogenated, for example using Raney Nickel as catalyst, to give an imine, which is reduced further, for example using sodium cyanoborohydride under controlled pH. A mixture of isomers are generated, in which the trans-trans is generally preferred.

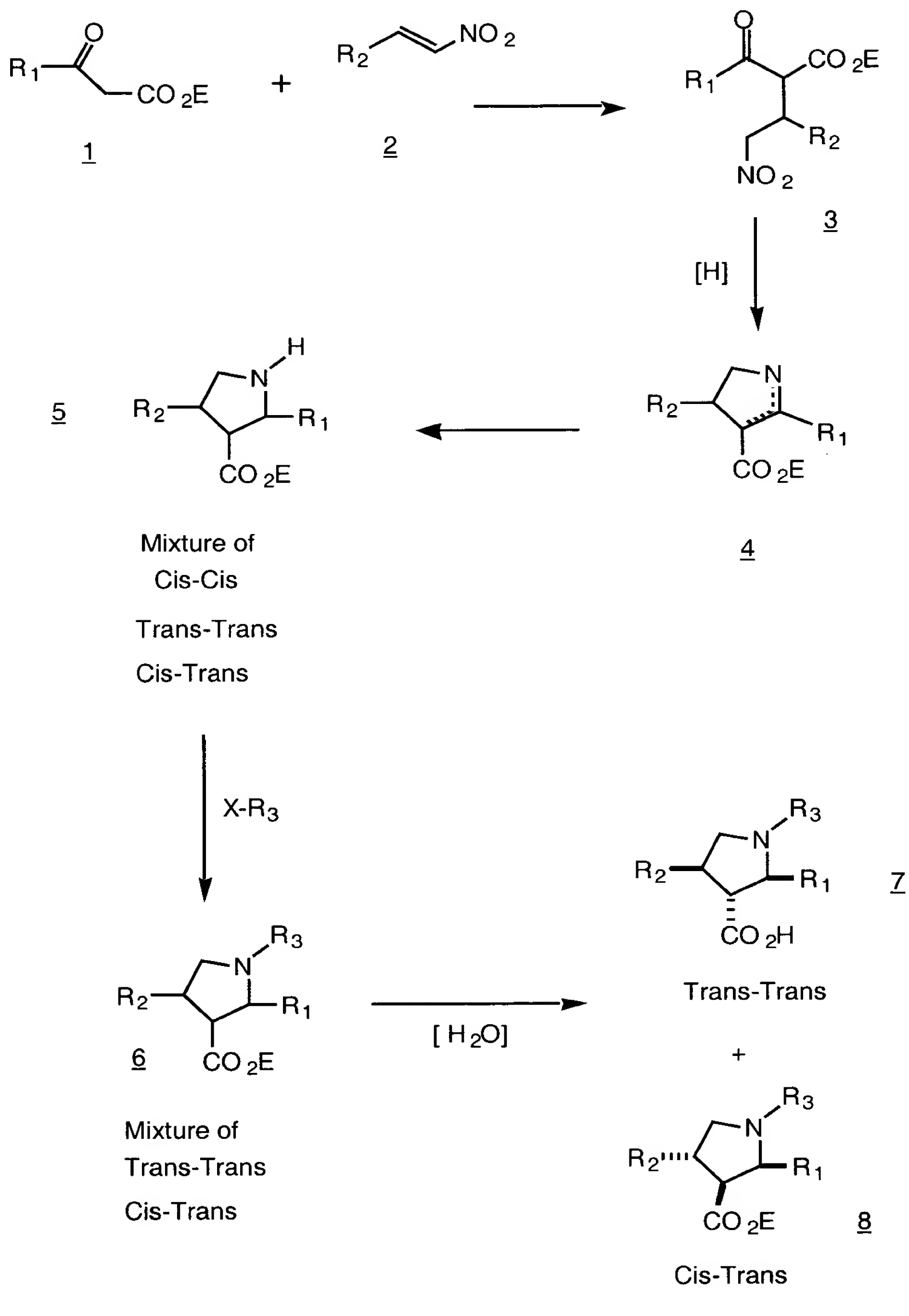
Scheme XIX describes several strategies for resolving the racemic pyrrolidines described above. Treatment with a chiral acid, for example (S)-(+)-mandelic acid, may provide a crystalline derivative, which can be further enriched through recrystallization. The salt may be washed with base to extract the resolving agent and return the optically active pyrrolidine product. Alternatively, the amino ester can be N-protected (for example with Boc-anhydride) and hydrolyzed (for example with sodium hydroxide) to give the corresponding N-protected amino acid. Activation of the acid, for example as the pentafluorophenyl ester, followed by coupling with a chiral nonracemic oxazolidinone anion, provides the corresponding acyloxazolidinone diastereomers, which may be separated chromatographically. Alcoholysis of one acyloxazolidinone diastereomer, followed by cleavage of the N-protecting group, returns an optically enriched amino ester. A similar transformation may be accomplished through coupling of the protected amino acid with a chiral nonracemic amino alcohol. After chromatographic separation of the resultant diastereomers, the amide is cleaved and the protecting group is removed to provide optically enriched product.

Optically active amino esters prepared as described above may be alkylated (Scheme XX) with a variety of electrophiles, for example dibutyl bromoacetamide, N-butyl,N-alkoxy bromoacetamide, N-(4-heptyl)-N-(3-methyl-4-fluorophenyl) bromoacetamide, or N-(Ω-hydroxyalkyl)-N-alkyl haloacetamide. Hydrolysis of the resultant ester, for example using sodium hydroxide in aqueous alcohol, provides the product.

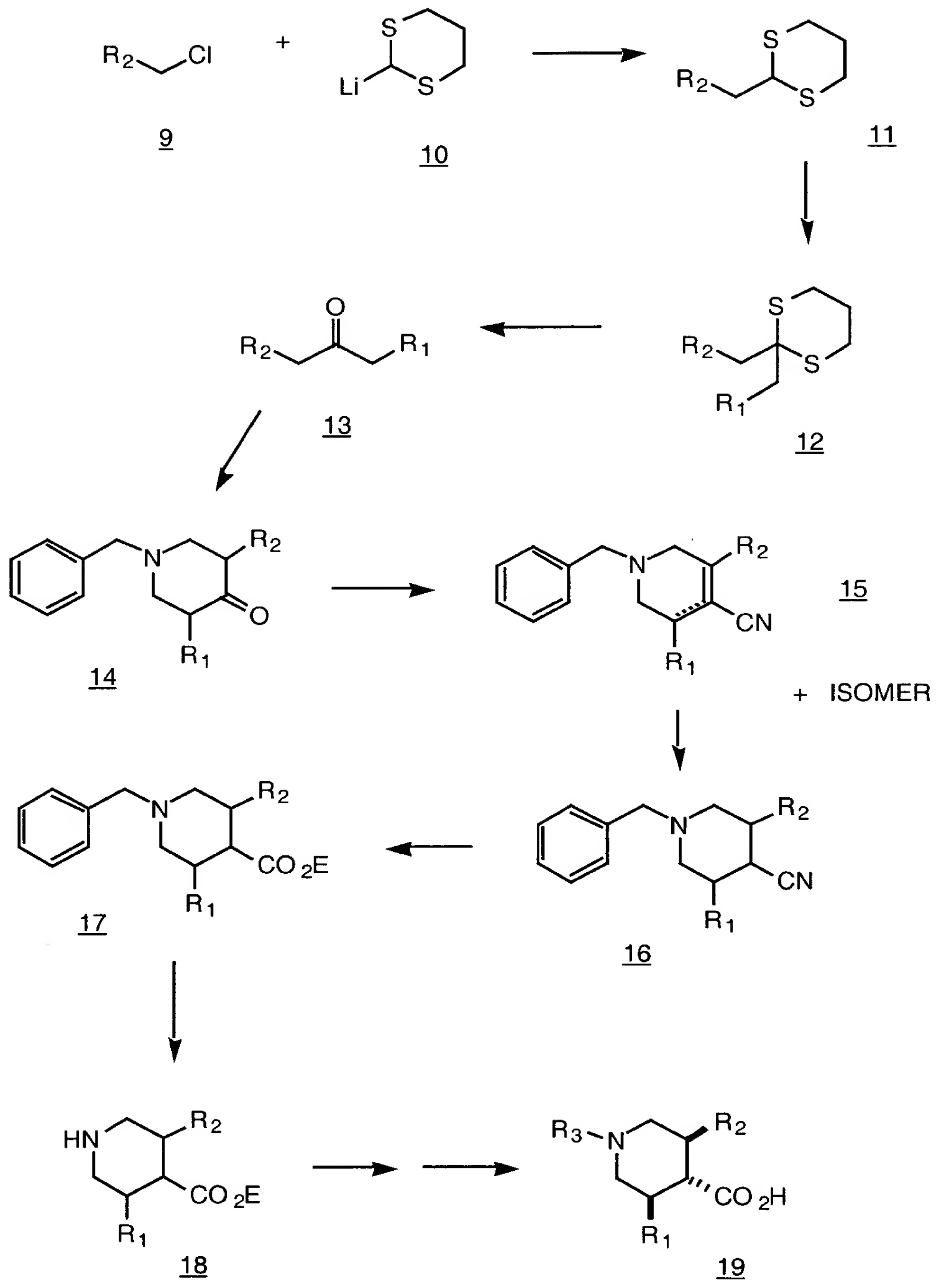
For one particular class of electrophile, N-(Ω-hydroxyalkyl)-N-alkyl haloacetamides, further transformations of the alkylation product are possible (Scheme XXI). Activation (for

example using methanesulfonyl chloride) of the alcohol, followed by displacement with halogen (for example, using lithium bromide) provides the corresponding halide. Displacement of halide with an amine, for example dimethylamine, provides the corresponding amino ester, which may be hydrolyzed as previously described to provide product.

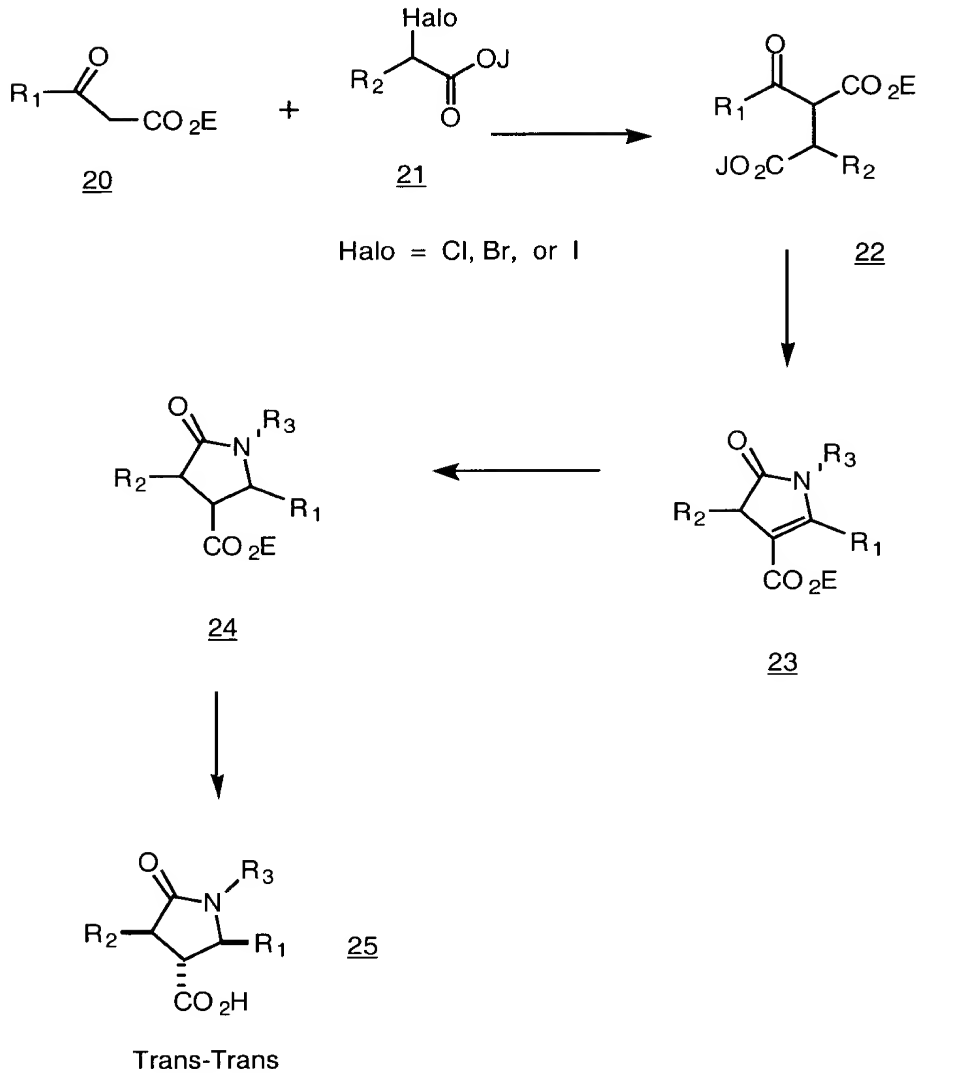
Scheme I


1
2
3
[H]
4
5
Mixture of
Cis-Cis
Trans-Trans
Cis-Trans
X-R3
6
Mixture of
Trans-Trans
Cis-Trans
[H2O]
7
Trans-Trans
+
8
Cis-Trans

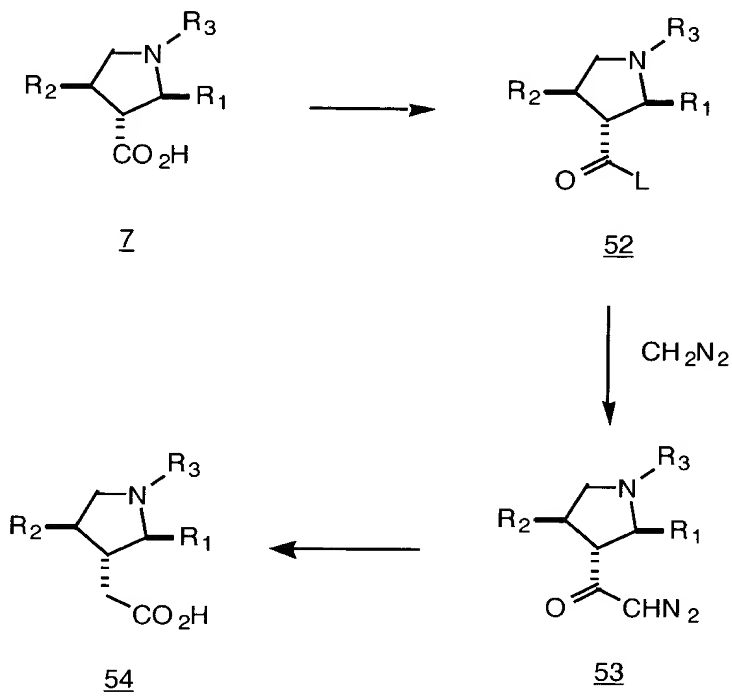
Scheme II



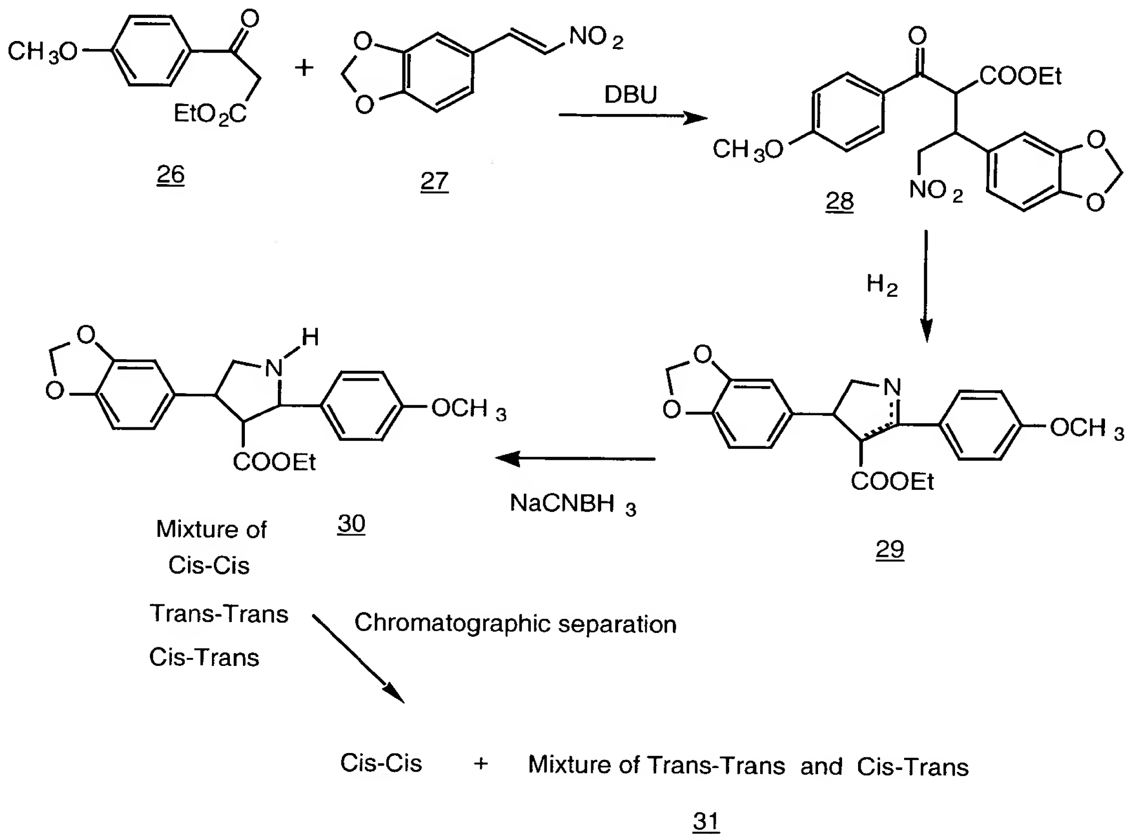
Scheme III



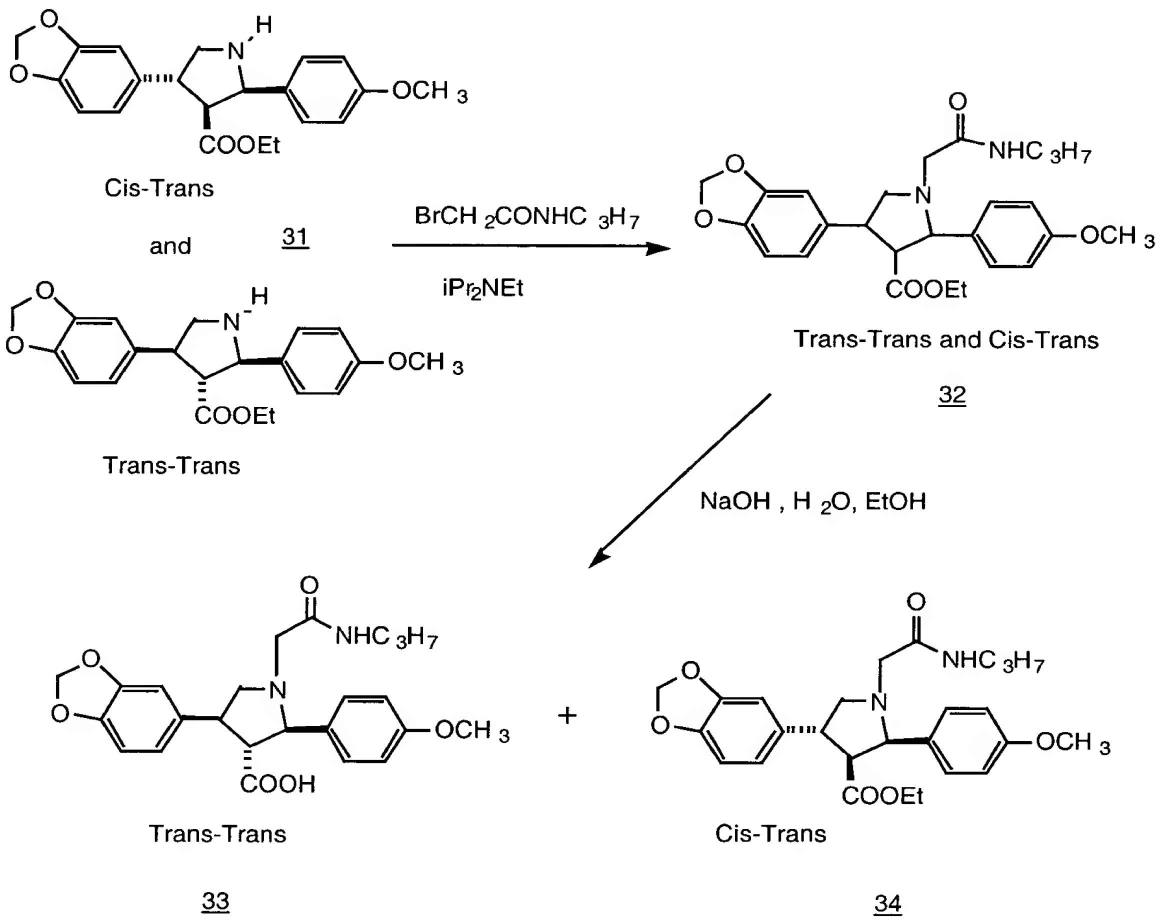
Scheme IV



Scheme V

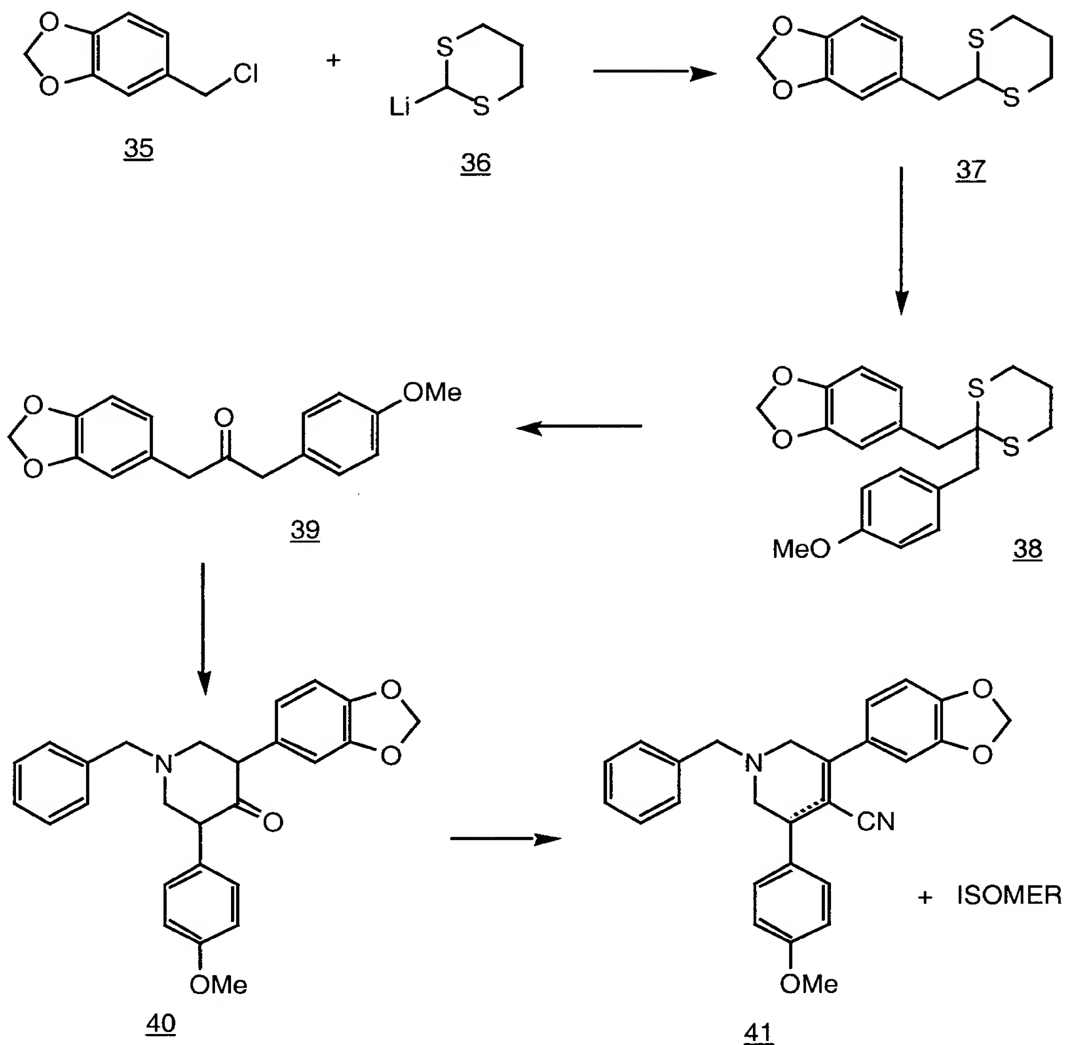

CH3O
O
EtO2C
26
+
NO2
27
DBU
O
COOEt
CH3O
NO2
28
H2
N
OCH3
COOEt
29
NaCNBH3
H
N
OCH3
COOEt
30
Mixture of
Cis-Cis
Trans-Trans
Cis-Trans
Chromatographic separation
Cis-Cis + Mixture of Trans-Trans and Cis-Trans
31

Scheme VI

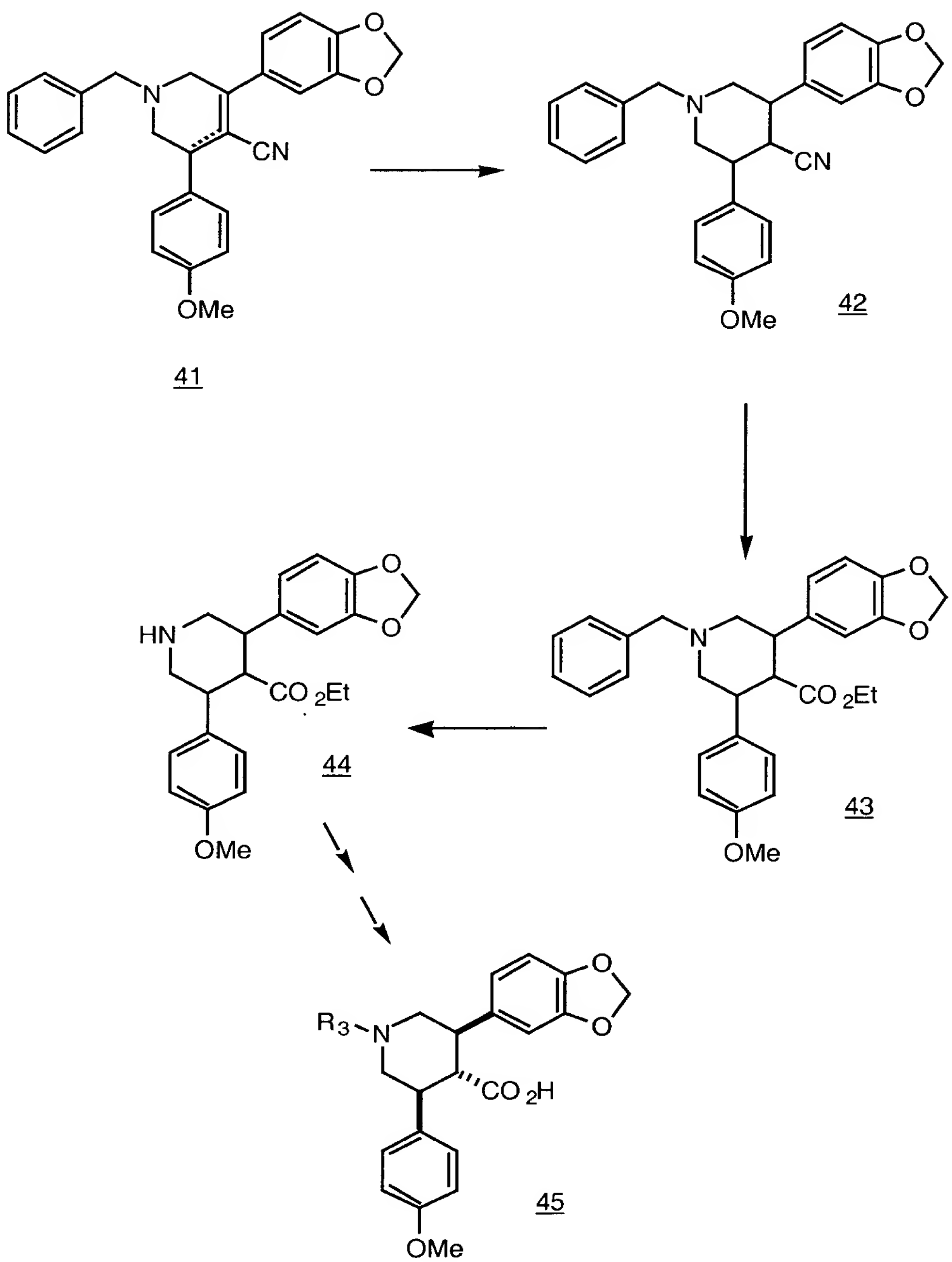


COOEt
Cis-Trans
and
31
Trans-Trans
BrCH $_2$CONHC $_3$H $_7$
iPr$_2$NEt
NHC $_3$H$_7$
OCH $_3$
Trans-Trans and Cis-Trans
32
NaOH , H $_2$O, EtOH
COOH
Trans-Trans
33
Cis-Trans
34

Scheme VII

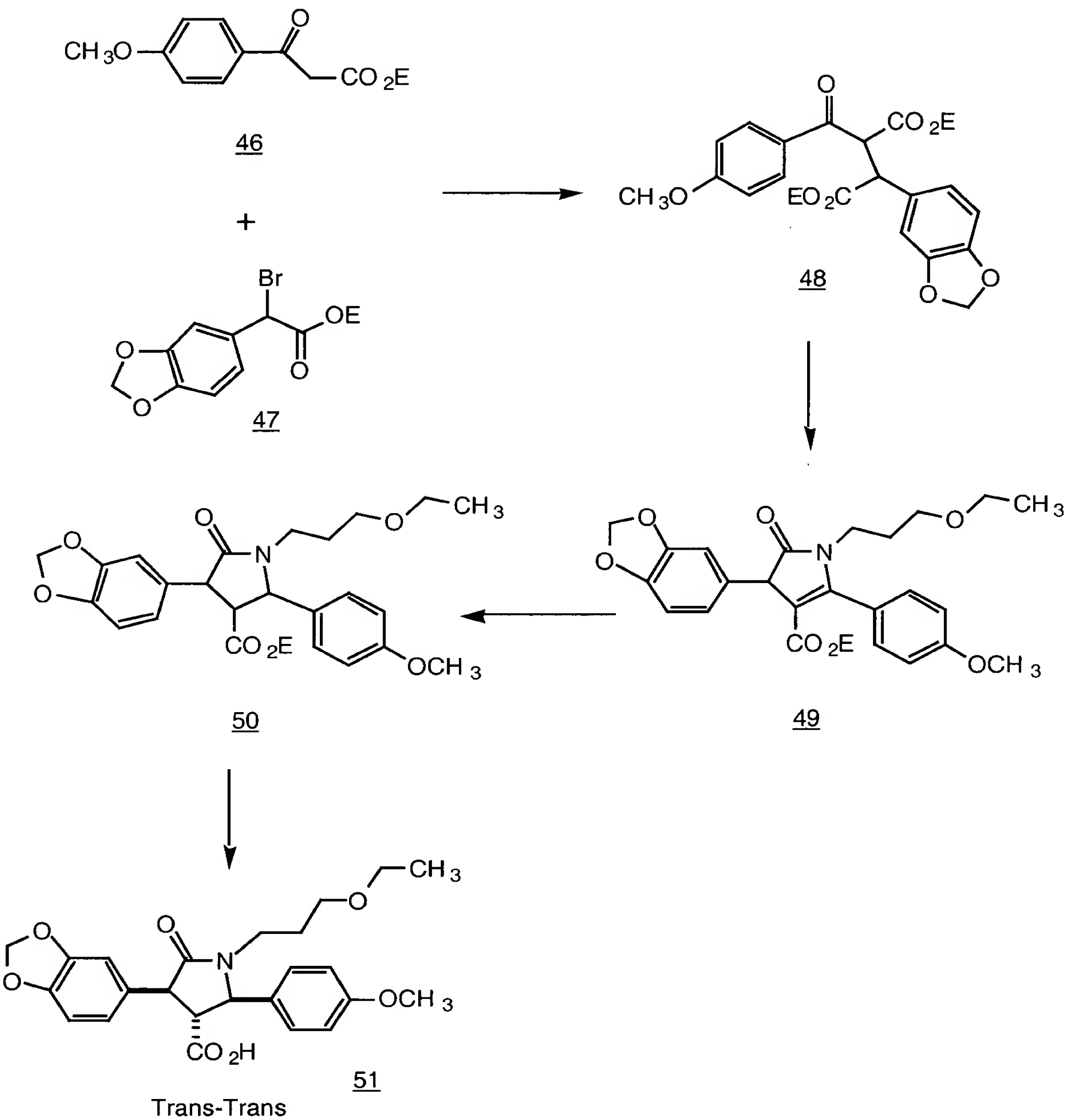


Scheme VII cont.

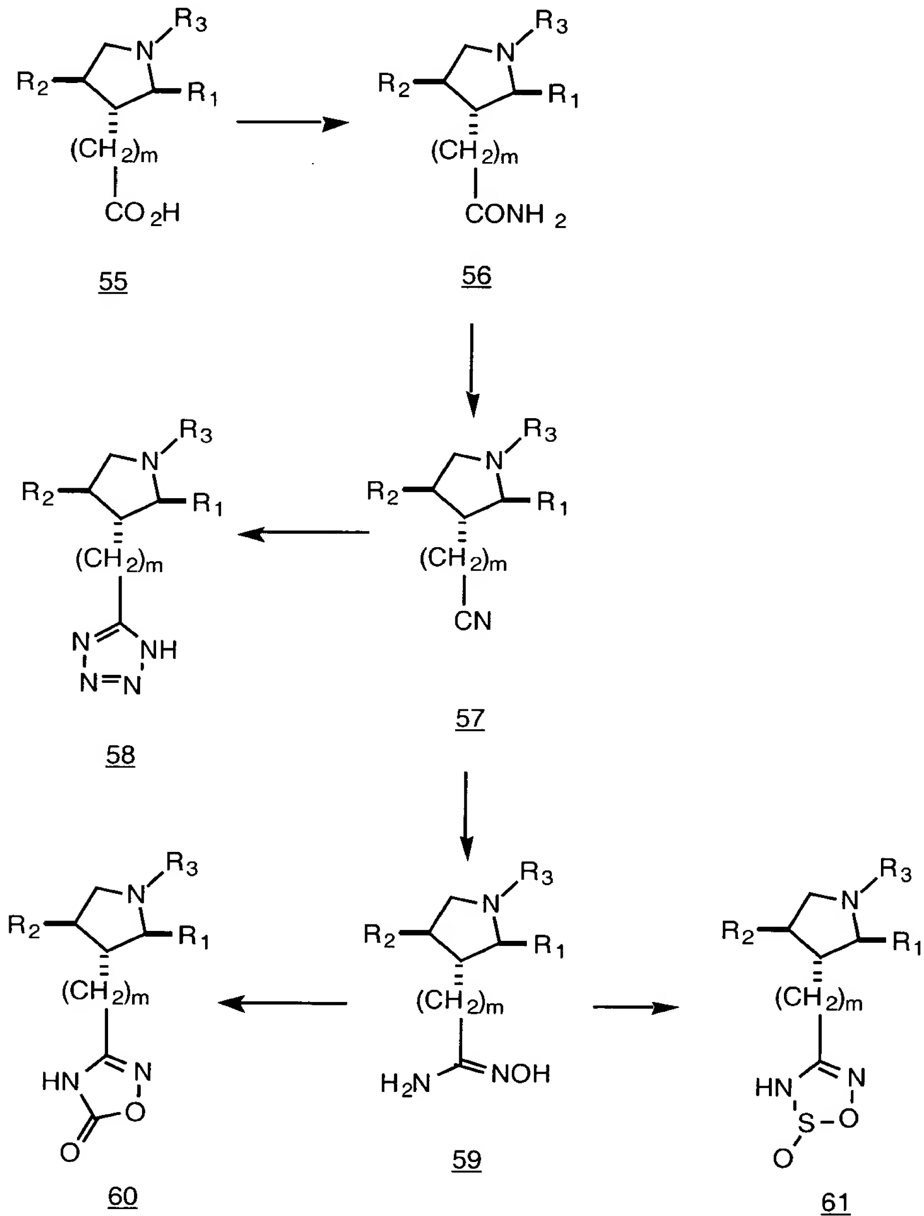


41 42 43 44 45

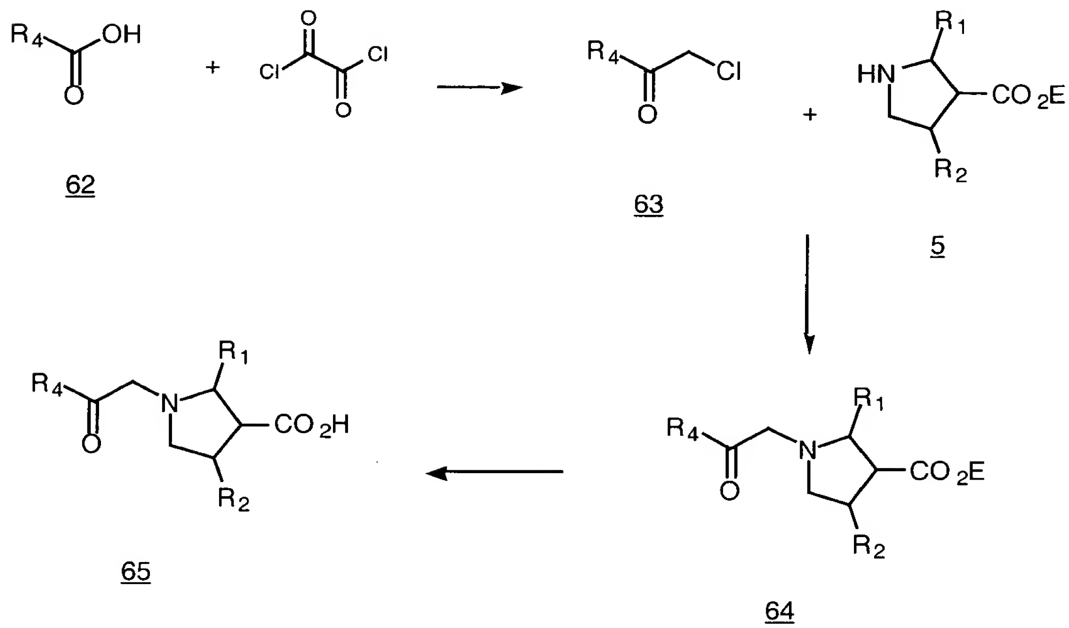
Scheme VIII


CH 3O
CO 2E
46
+
Br
OE
47
O
CO 2E
CH 3O
EO 2C
48
CH 3
CO 2E
OCH 3
49
50
CO 2H
51
Trans-Trans

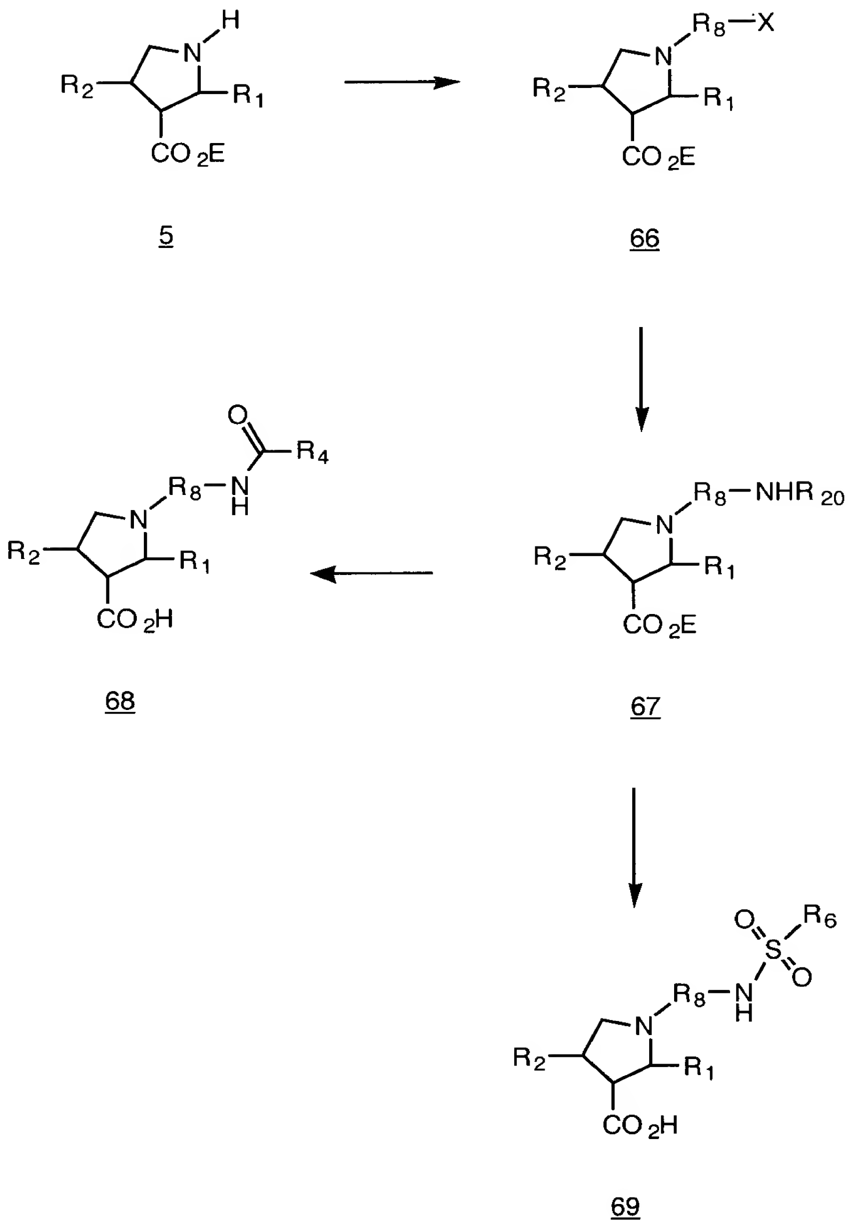
Scheme IX


R3
R2
R1
(CH2)m
CO2H
55
CONH2
56
CN
57
N
NH
N=N
58
H2N
NOH
59
HN
O
60
S-O
61

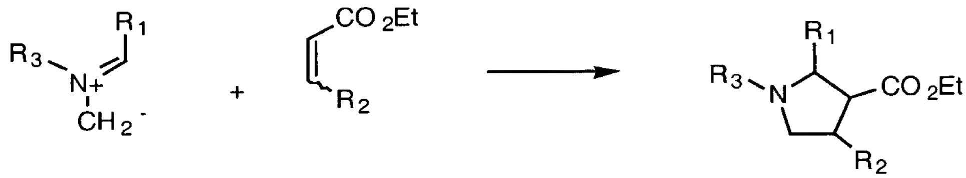
Scheme X


R4 OH
O
+
Cl Cl
O
O
R4 Cl
O
+
HN R1 CO2E R2
R4 N R1 CO2H R2
O
R4 N R1 CO2E R2
O
62
63
5
65
64

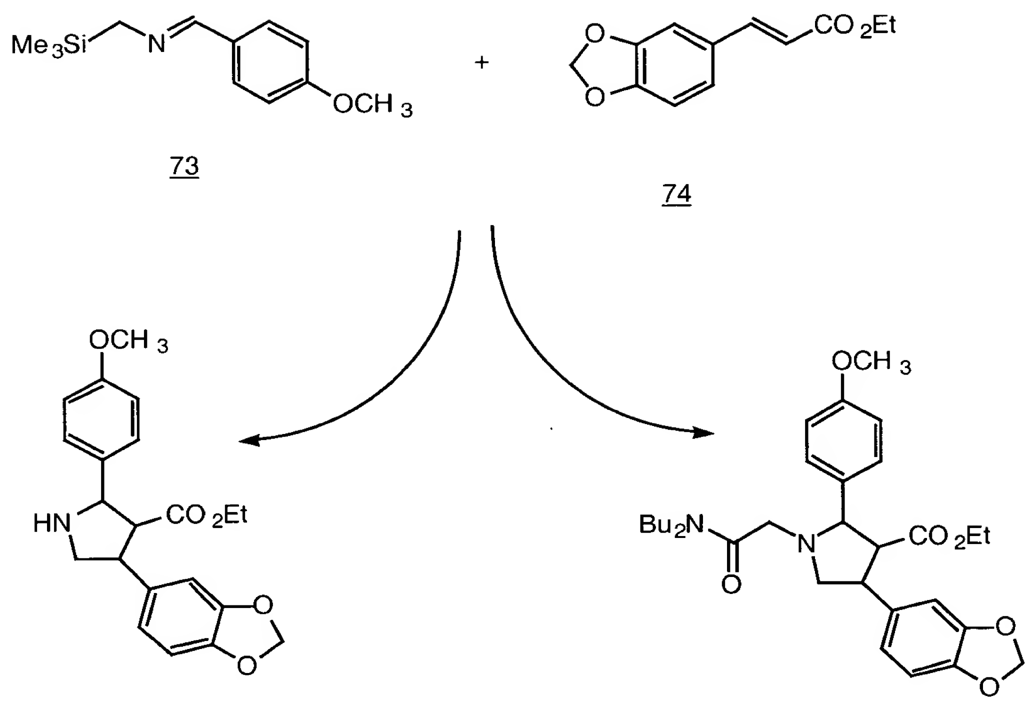
Scheme XI



Scheme XII



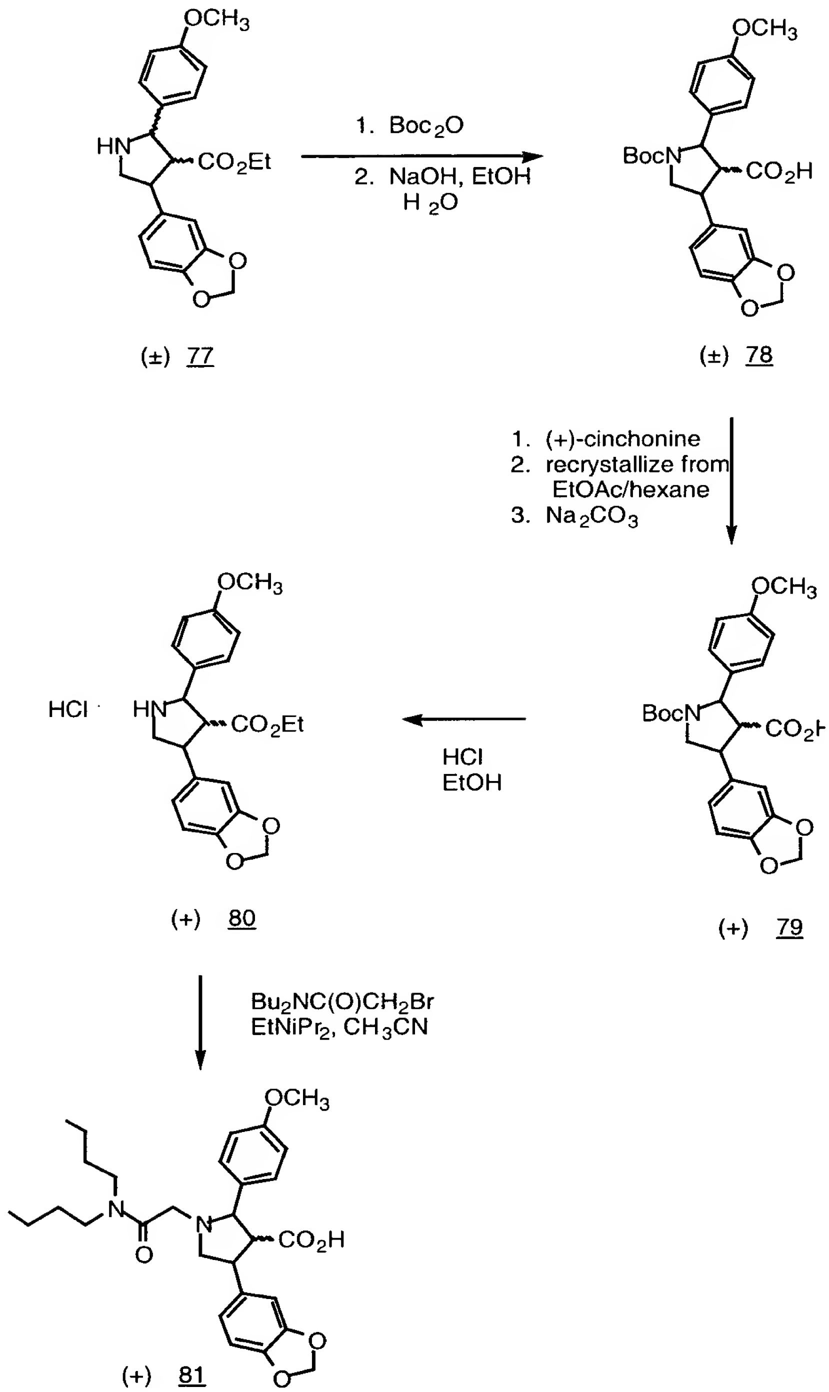
70 71 72



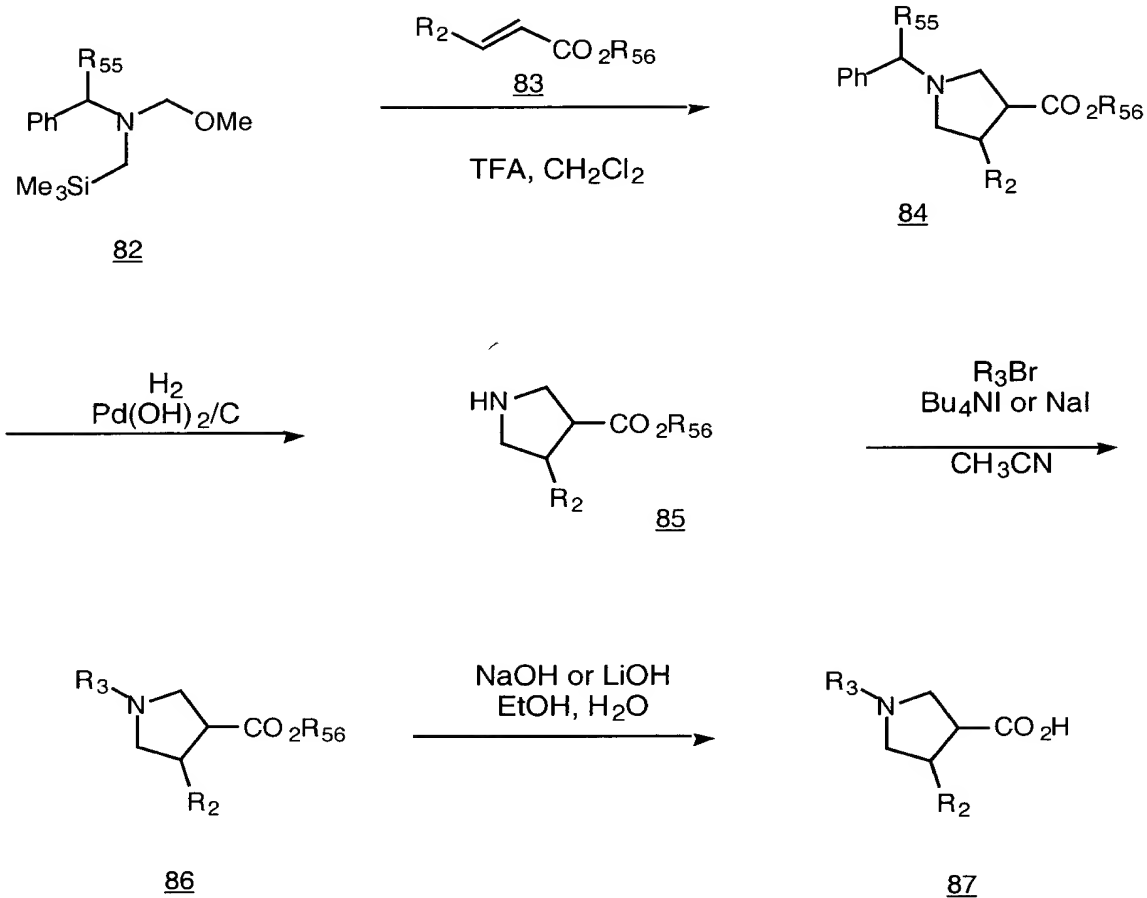
73 74

75 76

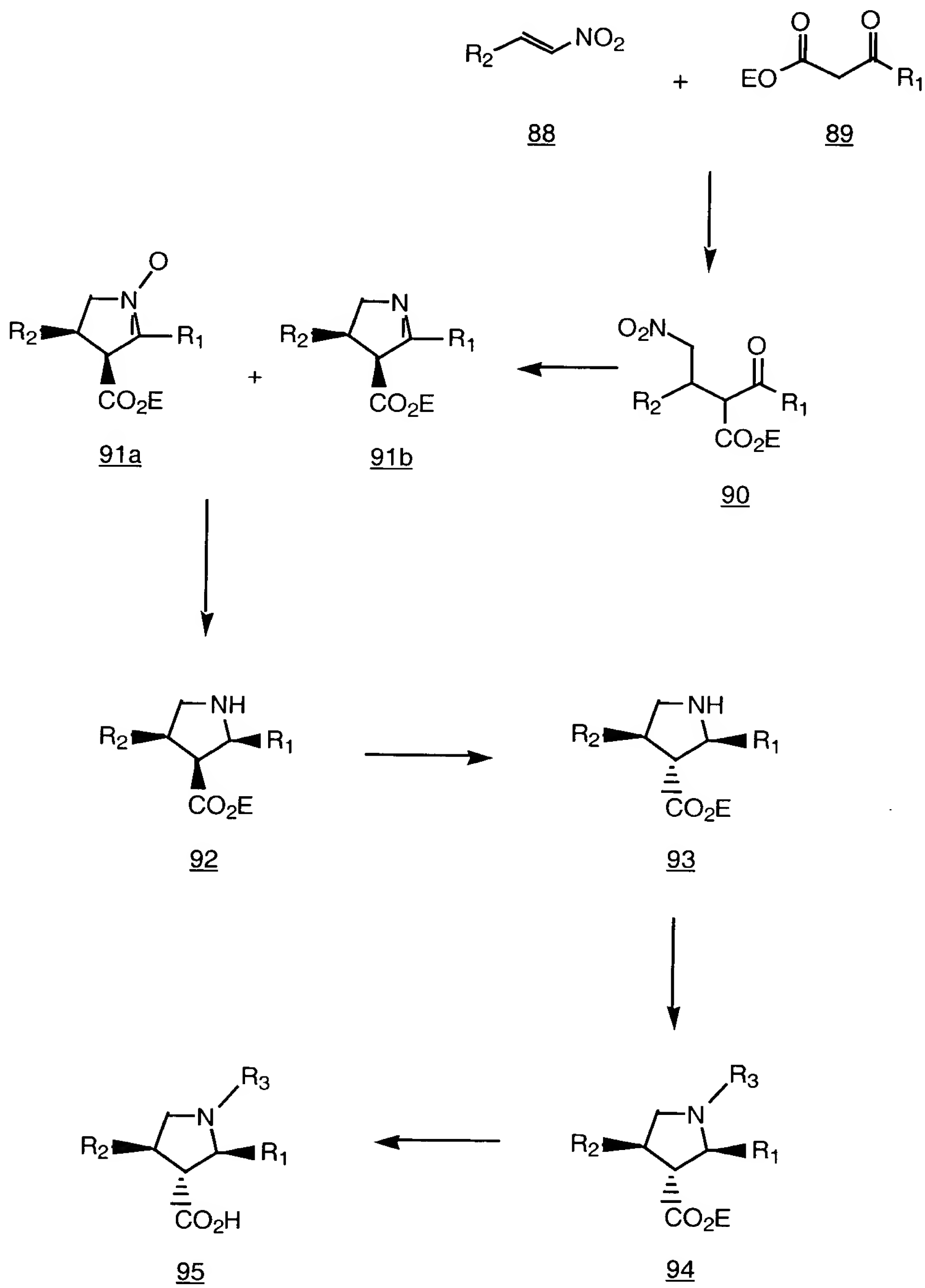
Scheme XIII


OCH3
HN
CO2Et
O
O
(±) 77
1. Boc2O
2. NaOH, EtOH
H 2O
BocN
CO2H
(±) 78
1. (+)-cinchonine
2. recrystallize from
EtOAc/hexane
3. Na2CO3
BocN
CO2H
(+) 79
HCl
EtOH
HCl · HN
CO2Et
(+) 80
Bu2NC(O)CH2Br
EtNiPr2, CH3CN
N
O
N
CO2H
(+) 81

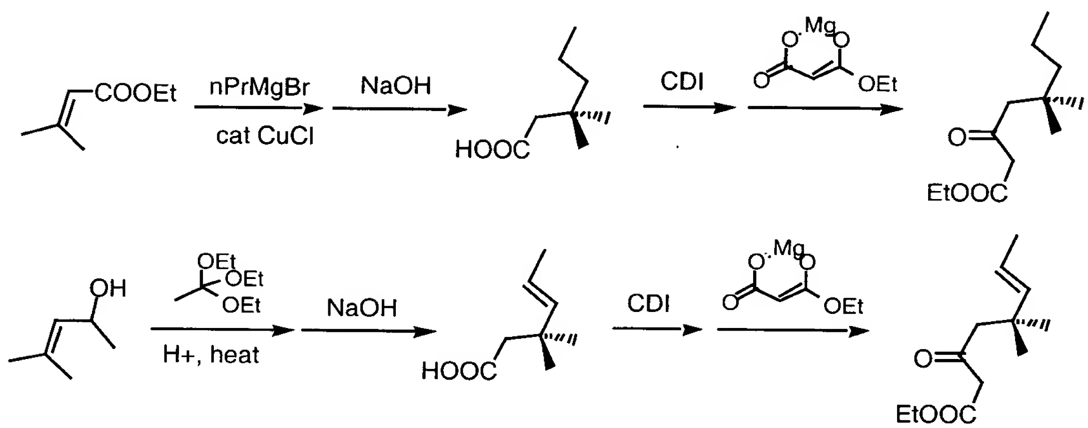
Scheme XIV


82
83
TFA, CH2Cl2
84
H2
Pd(OH)2/C
85
R3Br
Bu4NI or NaI
CH3CN
86
NaOH or LiOH
EtOH, H2O
87

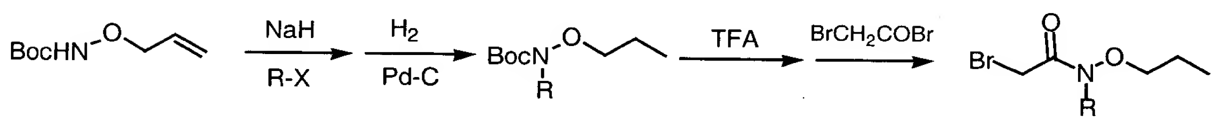
Scheme XV



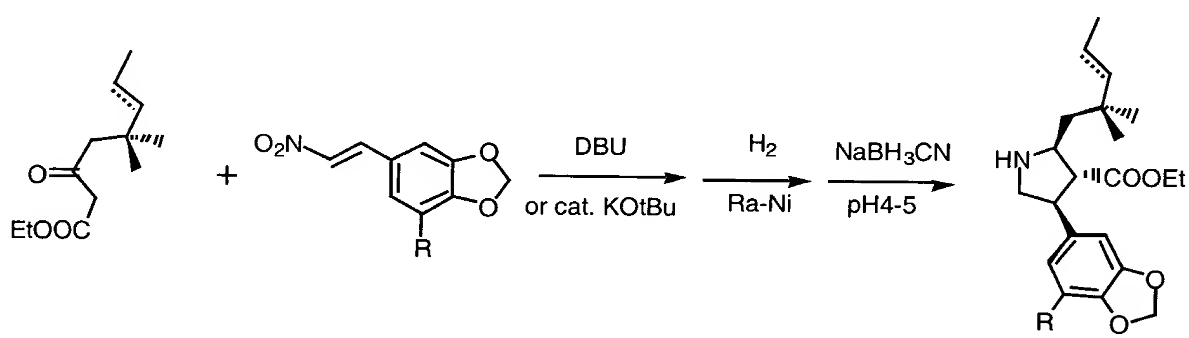
SCHEME XVI



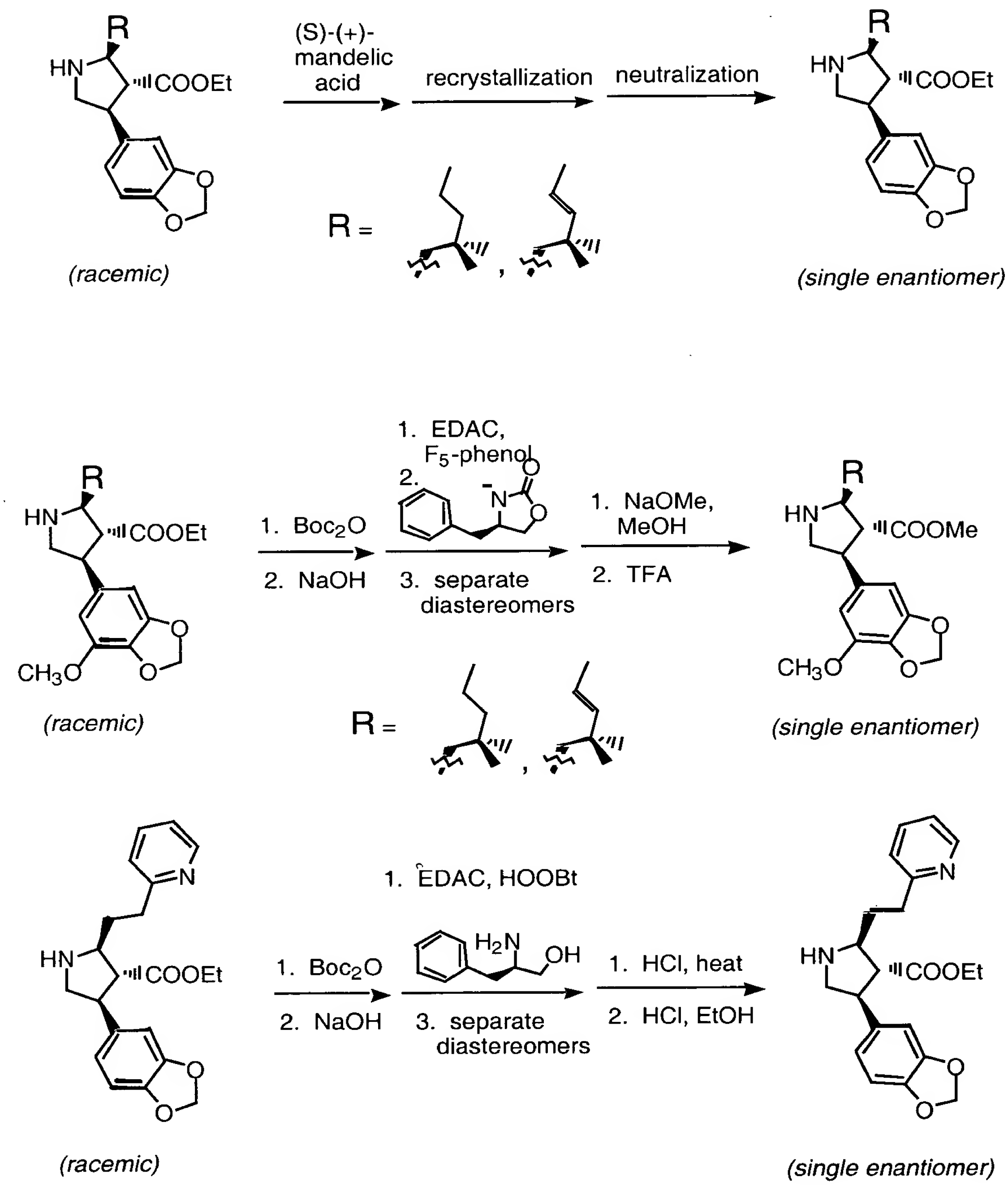
SCHEME XVII



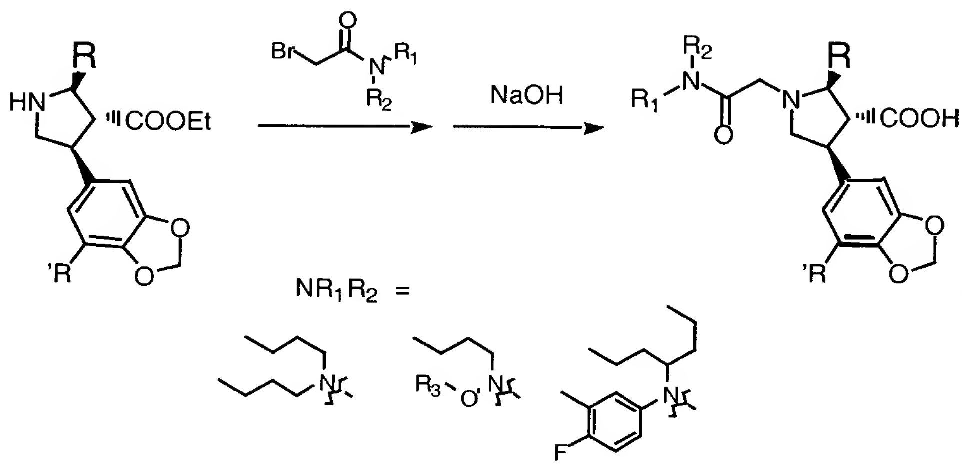
SCHEME XVIII



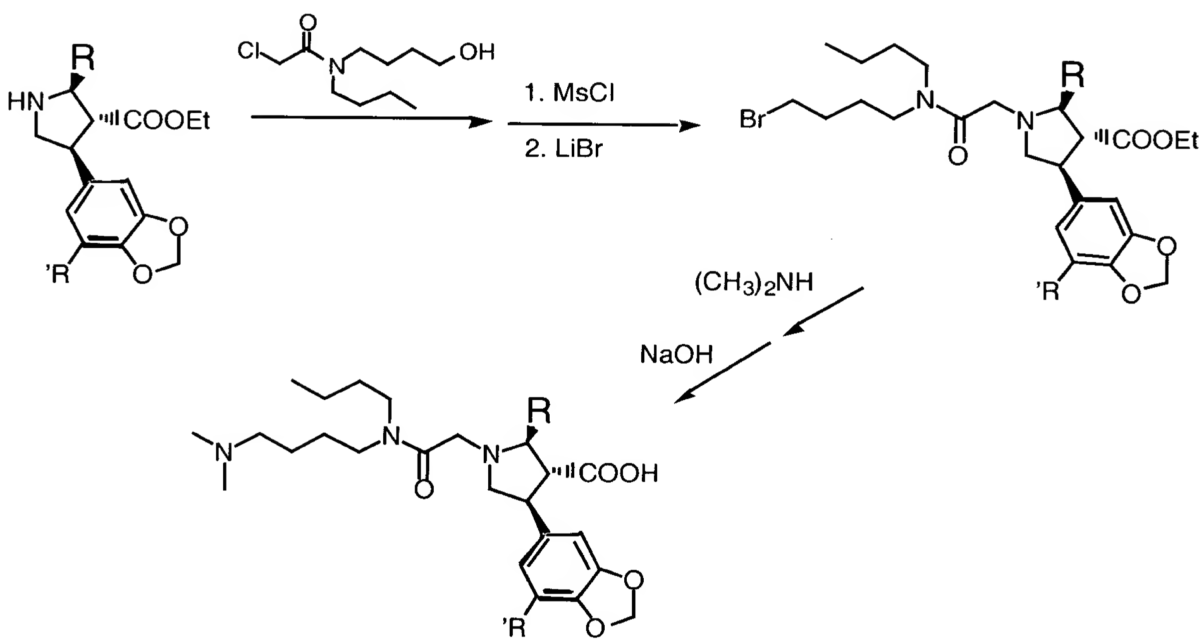
SCHEME XIX


HN
COOEt
R
(racemic)
(S)-(+)-mandelic acid
recrystallization
neutralization
R =
(single enantiomer)
CH3O
1. Boc2O
2. NaOH
1. EDAC, F5-phenol
2.
3. separate diastereomers
1. NaOMe, MeOH
2. TFA
COOMe
N
1. EDAC, HOOBt
H2N
OH
1. HCl, heat
2. HCl, EtOH

SCHEME XX



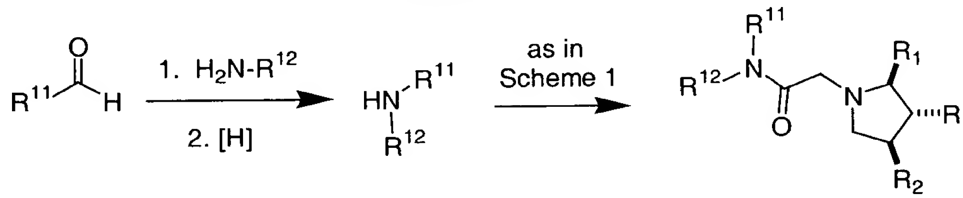
SCHEME XXI



Other amines may be prepared according to Scheme XXII. An aryl aldehyde or ketone (aldehyde shown), which may be acquired commercially or prepared, for example, through a Friedel-Crafts acylation of a benzene derivative with an acy halide, is reacted with an amine, for example ammonia, hydroxylamine or the like. The resultant imine is reduced,

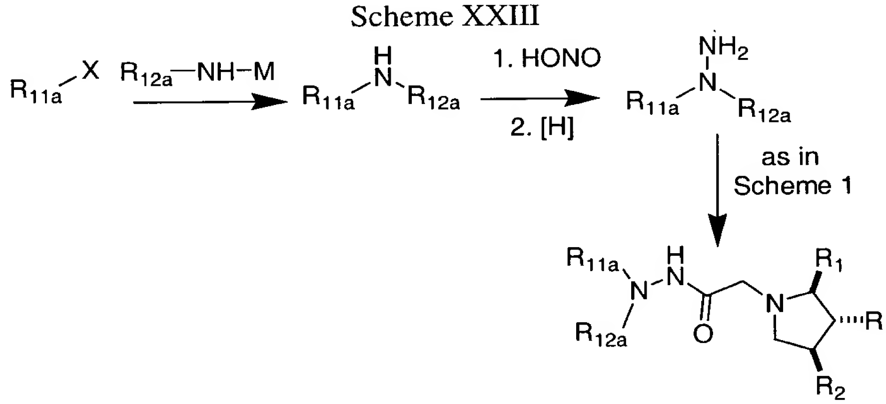
for example using sodium borohydride or sodium cyanoborohydride or a metal like zinc or tin or the like, to give the corresponding optionally substituted carbinylamine, which is converted to the target compound according to the procedures described above.

Scheme XXII

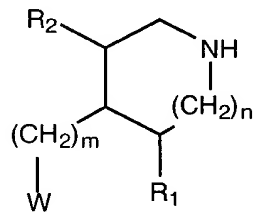


Still other amines may be prepared according to Scheme XXIII. An optionally substituted aryl halide (R_{11a} is the optionally substituted aryl and X is bromo or iodo) is reacted with a metallated amine (for example, lithium tert-butylamide, or sodium benzylamide, or the like) to provide an optionally substituted aniline. This compound is reacted with an oxidized nitrogen compound, for example nitrous acid or the like, and the resultant compound is reduced using a metal like zinc or tin or palladium or the like to provide an N,N-disubstituted hydrazine, which is converted to the target compound according to the procedures described above.

Scheme XXIII



Compounds which are useful as intermediates for the preparation of compounds of the invention are:



(III)

wherein n is 0 or 1;

m is 0 to 6;

W is (a) $-C(O)_2-G$ where G is hydrogen or a carboxy protecting group, (b) $-PO_3H_2$,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ where R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

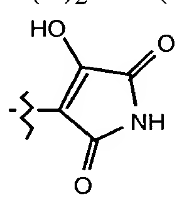
(i) hydroxy,

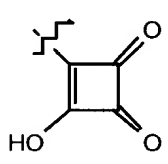
(j) alkoxy,

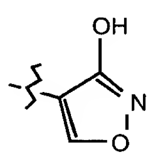
(k) sulfonamido,

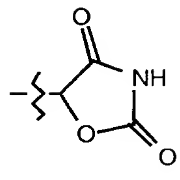
(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or dialkylamino,

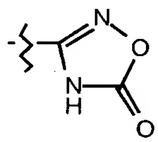
(m) $-S(O)_2NHC(O)R_{16}$,

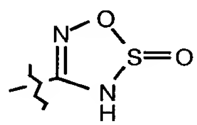
(n) ,

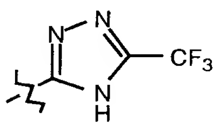
(o) ,

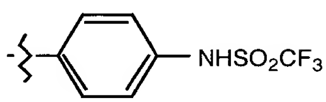
(p) ,

(q)  ,

(r)  ,

(s)  ,

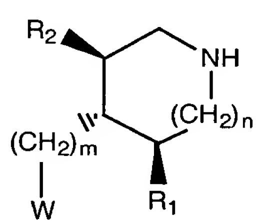
(t)  , or

(u)  ; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N$-R_{cc}- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

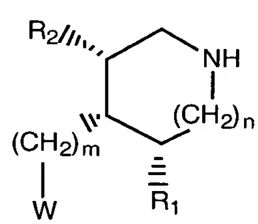
or a salt thereof;

or a compound of the formula:



(IV)

or



(V)

wherein n is 0 or 1;

m is 0 to 6;

W is (a) $-C(O)_2-G$ where G is hydrogen or a carboxy protecting group, (b) $-PO_3H_2$,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ where R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

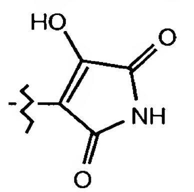
(i) hydroxy,

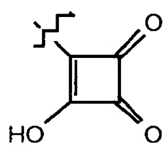
(j) alkoxy,

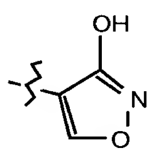
(k) sulfonamido,

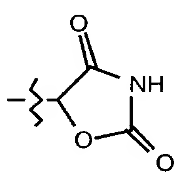
(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or dialkylamino,

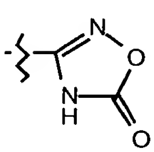
(m) $-S(O)_2NHC(O)R_{16}$,

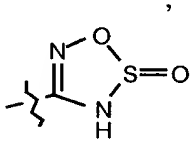
(n)  ,

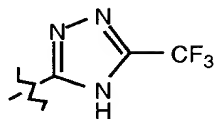
(o)  ,

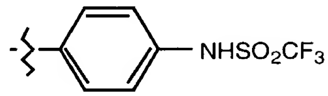
(p)  ,

(q)  ,

(r)  ,

(s)  ,

(t)  , or

(u)  ; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}-$ wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

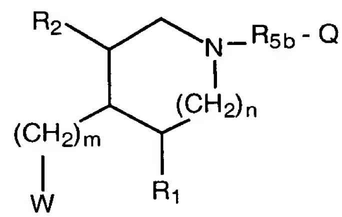
or a salt thereof.

Preferred intermediates include compounds of formula (III), (IV) and (V) wherein m is zero or 1;
W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group,
and R_1 and R_2 are as defined above; or
the substantially pure (+)- or (-)-isomer thereof.

Particularly preferred intermediates are compounds of formula (III), (IV) and (V) wherein
n and m are both 0;
W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group;
and R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy (ix) aryalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, and (xiii) alkylsulfonylamidoalkyl, and R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl,

1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofurnayl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen; or
the substantially pure (+)- or (-)-isomer thereof.

Other compounds which are useful as intermediates for the preparation of compounds of the invention are:



(VI)

wherein n is 0 or 1;

m is 0 to 6;

R_{5b} is alkylene;

Q is a leaving group;

W is (a) $-C(O)_2-G$ where G is hydrogen or a carboxy protecting group, (b) $-PO_3H_2$,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ where R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

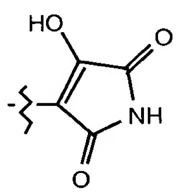
(i) hydroxy,

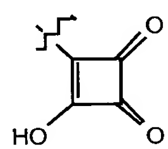
(j) alkoxy,

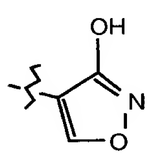
(k) sulfonamido,

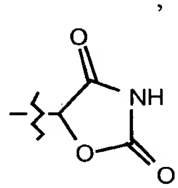
(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or dialkylamino,

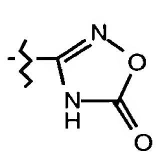
(m) $-S(O)_2NHC(O)R_{16}$,

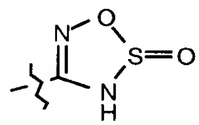
(n) ,

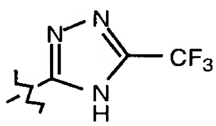
(o) ,

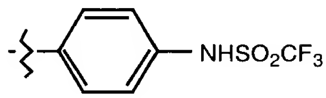
(p) ,

(q) ,

(r) ,

(s)  ,

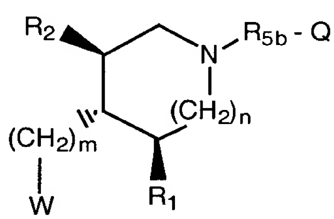
(t)  , or

(u)  ; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N\text{-}R_{cc}\text{-}$ wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

or a salt thereof;

or a compound of the formula:



(VII)

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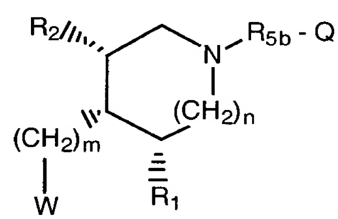


(VIII)

wherein n is 0 or 1;

m is 0 to 6;

R_{5b} is alkylene;

Q is a leaving group;

W is (a) $-C(O)_2-G$ where G is hydrogen or a carboxy protecting group, (b) $-PO_3H_2$,

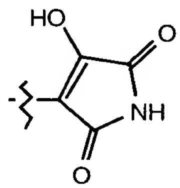
(c) $-P(O)(OH)E$ where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ where R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,
(h) tetrazolyl,
(i) hydroxy,
(j) alkoxy,
(k) sulfonamido,
(l) -C(O)NHS(O)$_2$R$_{16}$ where R$_{16}$ is loweralkyl, haloalkyl, phenyl or dialkylamino,
(m) -S(O)$_2$NHC(O)R$_{16}$,

(n) 

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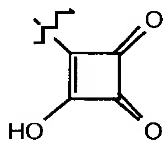
(o) 

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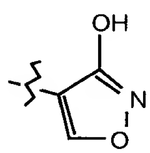
(p) 

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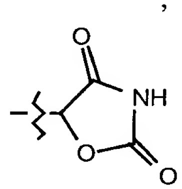
(q) 

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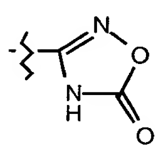
(r) 

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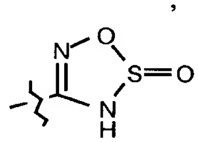
(s) 

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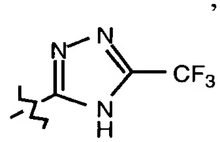
(t) 

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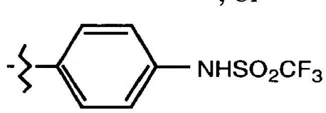
(u) 

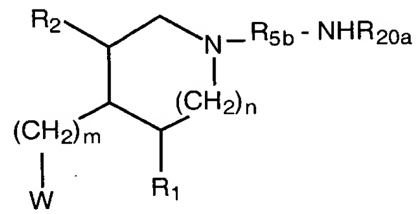
; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and
$(R_{aa})(R_{bb})N-R_{cc}-$ wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;
or a salt thereof.

Preferred intermediates include compounds of formula (VI), (VII) and (VIII) wherein
m is zero or 1;
R_{5b} is alkylene;
Q is a leaving group;
W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group,
and R_1 and R_2 are as defined above; or
the substantially pure (+)- or (-)-isomer thereof.

Particularly preferred intermediates are compounds of formula (VI), (VII) and (VIII) wherein
n and m are both 0;
R_{5b} is alkylene;
Q is a leaving group;
W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group;
and R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) aryalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, and (xiii) alkylsulfonylamidoalkyl, and R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofurnayl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen; or
the substantially pure (+)- or (-)-isomer thereof.

Other compounds which are useful as intermediates for the preparation of compounds of the invention are:



(IX)

wherein n is 0 or 1;

m is 0 to 6;

R_{5b} is alkylene;

R_{20a} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;

W is (a) $-C(O)_2-G$ where G is hydrogen or a carboxy protecting group, (b) $-PO_3H_2$,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ where R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

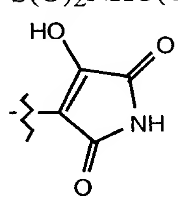
(i) hydroxy,

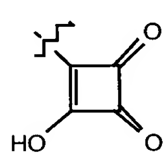
(j) alkoxy,

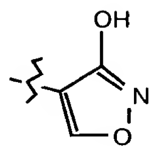
(k) sulfonamido,

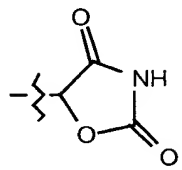
(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or dialkylamino,

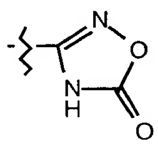
(m) $-S(O)_2NHC(O)R_{16}$,

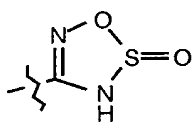
(n)  ,

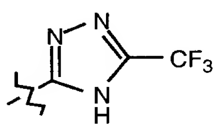
(o)  ,

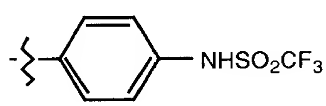
(p)  ,

(q)  ,

(r)  ,

(s)  ,

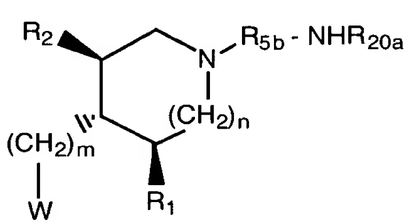
(t)  , or

(u)  ; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

or a salt thereof;

or a compound of the formula:



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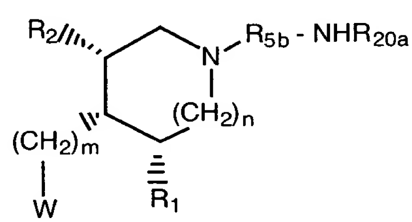
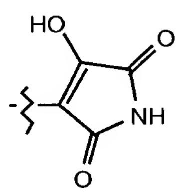


(X) (XI)

wherein n is 0 or 1;
m is 0 to 6;
R_{5b} is alkylene;
R_{20a} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;
W is (a) $-C(O)_2-G$ where G is hydrogen or a carboxy protecting group, (b) $-PO_3H_2$,
(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,
(d) -CN,
(e) $-C(O)NHR_{17}$ where R_{17} is loweralkyl,
(f) alkylaminocarbonyl,
(g) dialkylaminocarbonyl,
(h) tetrazolyl,
(i) hydroxy,
(j) alkoxy,
(k) sulfonamido,
(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or dialkylamino,
(m) $-S(O)_2NHC(O)R_{16}$,

(n) 

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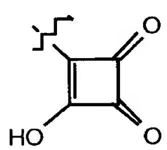
(o) 

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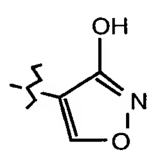
(p) 

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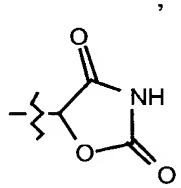
(q) 

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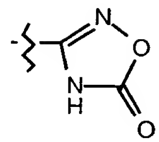
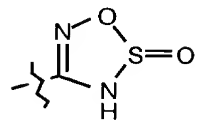
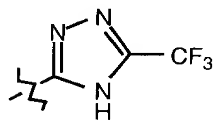
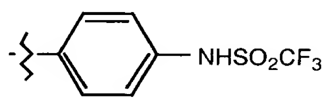
(r)  ,

(s)  ,

(t)  , or

(u)  ; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N$-R_{cc}- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

or a salt thereof.

Preferred intermediates include compounds of formula (IX), (X) and (XI) wherein

m is zero or 1;

R_{5b} is alkylene;

R_{20a} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;

W is -CO_2-G wherein G is hydrogen or a carboxy protecting group,

and R_1 and R_2 are as defined above; or

the substantially pure (+)- or (-)-isomer thereof.

Particularly preferred intermediates are compounds of formula (IX), (X) and (XI) wherein

n and m are both 0;

R_{5b} is alkylene;

R_{20a} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;

W is $-CO_2$-G wherein G is hydrogen or a carboxy protecting group;
and R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, and (xiii) alkylsulfonylamidoalkyl, and R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofurnayl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen; or
the substantially pure (+)- or (-)-isomer thereof.

The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept. The following abbreviations are used: Boc for tert-butyloxycarbonyl, Cbz for benzyloxycarbonyl, DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene, EDCI for 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride, EtOAc for ethyl acetate, EtOH for ethanol, HOBt for 1-hydroxybenzotriazole, Et_3N for triethylamine, TFA for trifluoroacetic acid and THF for tetrahydrofuran.

Example 1

trans,trans- 2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 1A

Ethyl 2-(4-methoxybenzoyl)-4-nitromethyl-3-(1,3-benzodioxole-5-yl)butyrate

To ethyl (4-methoxybenzoyl)acetate (23.0 g, 0.104 mol), prepared by the method of Krapcho *et al.*, Org. Syn. 47, 20 (1967), and 5-(2-nitrovinyl)-1,3-benzodioxole (17.0 g, 0.088 mol) dissolved in 180 mL of toluene and heated to 80 °C was added 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU, 0.65 g) with stirring. The mixture was heated until all the nitro starting material dissolved. The solution was stirred without heating for 30 minutes (min) and then an additional 0.65 g of DBU was added. After stirring an additional 45 minutes, thin layer chromatography (5% ethyl acetate in methylene chloride) indicated the absence of nitro starting material. Toluene (200 mL) was added, and the organic phase was washed with

dilute hydrochloric acid and NaCl solution. The organic phase was dried over sodium sulfate and then concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 3:1 hexane-ethyl acetate to give 21.22 g of the desired product as a mixture of isomers and 9.98 g. of recovered ethyl (4-methoxybenzoyl)acetate.

Example 1B
Ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-4,5-dihydro-3H-pyrrole-3-carboxylate

The compound resulting from Example 1A (21 g) in 500 mL of ethanol was hydrogenated under 4 atmospheres of hydrogen pressure using a Raney nickel 2800 catalyst (51 g). (The Raney nickel was washed with ethanol three times before use.) The catalyst was removed by filtration, and the solution was concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 8.5% ethyl acetate in methylene chloride to give 12.34 g of the desired product.

Example 1C
Ethyl 2-(4-methoxyphenyl-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate) as a mixture of *cis-cis*; *trans,trans*; and *cis,trans*-isomers

The compound resulting from Example 1B (11.89 g, 0.324 mol) was dissolved in 27 mL of tetrahydrofuran and 54 mL of ethanol. Sodium cyanoborohydride (2.35 g, 0.374 mol) and 5 mg bromocresol green were added. To this blue solution was added dropwise a solution of 1:2 concentrated HCl in ethanol at such a rate that the color was kept at light yellow-green. After the yellow color persisted without additional HCl, the solution was stirred an additional 20 minutes. The solution was concentrated *in vacuo* and then partitioned between chloroform and an aqueous potassium bicarbonate solution. The organic phase was separated, dried over sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 85:15 ethyl acetate-hexane to give 5.96 g. of a mixture of 64% *trans,trans*-compound and 34% *cis,trans*-compound. Further elution with pure ethyl acetate gave 0.505 g of an unknown solid followed by 3.044 g of pure *cis,cis*-compound.

Example 1D
trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The mixture of 64% *trans,trans*- and 34% *cis,trans*-pyrrolidines (the mixture resulting from Example 1C) (5.72 g, 15.50 mmol), ethyldiisopropylamine (4.20 g, 32.56 mmol), and N-propyl bromoacetamide (3.42 g, 19.0 mmol), prepared by the method of Weaver, W.E. and

Whaley, W.M., J. Amer. Chem. Soc., 69: 515 (1947), in 30 mL of acetonitrile was heated at 50 °C for 1 hour. The solution was concentrated *in vacuo*. The residue was dissolved in toluene, shaken with potassium bicarbonate solution, dried over sodium sulfate and concentrated *in vacuo* to give 7.16 g of product as a mixture of *trans,trans*- and *cis,trans*-ethyl esters.

This mixture was dissolved in a solution of 50 mL of ethanol and 15 mL of water containing 5.00 g of sodium hydroxide and stirred for 3 hours at room temperature. The solution was concentrated *in vacuo* and 60 mL of water added. The mixture was extracted with ether to remove the unreacted *cis,trans*- ethyl ester. The aqueous phase was treated with hydrochloric acid until slightly cloudy. It was then further neutralized with acetic acid to give the crude acid product. The crude product was filtered and purified by dissolving it in tetrahydrofuran, drying over sodium sulfate, concentrating *in vacuo*, and crystallizing from ether to give 3.230 g of the title compound. m.p. 151-153 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.87 (t, J = 7 Hz, 3H), 1.49 (sextet, J = 7 Hz, 2H), 2.84 (d, J = 16 Hz, 1H), 2.95-3.20 (m, 4H), 3.20 (d, J = 16 Hz, 1H), 3.34-3.42 (m, 1H), 3.58-3.66 (m, 1H), 3.78 (s, 3H), 3.88 (d, J = 10 Hz, 1H), 5.92 (s, 2H), 6.75 (d, J = 8 Hz, 1H), 6.86 (dd, J= 8 Hz, J = 1 Hz, 1H), 6.90 (d, J = 9 Hz, 2H), 7.02 (d, J = 1 Hz, 1H), 7.40 (d, J = 9 Hz, 2H).

Example 2

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the method described in Example 1D, 300 mg of the mixture of 64% *trans,trans*- and 34% *cis,trans*-pyrrolidines (the mixture resulting from Example 1C), 220 mg of diisopropylethylamine and 184 mg iodoacetamide were reacted at 45 °C in 1 mL acetonitrile to give 291 mg of a mixture of *trans,trans*- and *cis,trans*- N-alkylated esters. A portion (270 mg.) was hydrolyzed with 200 mg NaOH in 1 mL of water and 3 mL of ethanol; a chloroform extraction was used to remove the unreacted *cis,trans*- ethyl ester. The isolation and purification procedures described in Example 1D were used to give 134 mg of the title compound. m.p. 246-248 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.61 (d, J = 16 Hz, 1H), 2.71 (t, J = 9 Hz, 1H), 2.90 (t, J = 9 Hz, 1H), 2.98 (d, J = 16 Hz, 1H),3.25-3.35 (m, 1H), 3.45-3.55 (m, 1H), 3.71 (s, 3H), 3.75 (d, J = 10 Hz, 1H), 6.00 (s, 2H), 6.81 (s, 2H), 6.90 (d, J = 8 Hz, 2H), 7.10 (s, 1H), 7.17 (s, 1H), 7.34 (s, 1H), 7.38 (d, J = 8 Hz, 2H).

Example 3

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(4-fluorobenzyl)-pyrrolidine-3-carboxylic acid

Using the method described in Example 1D, 300 mg of the mixture of 64% *trans,trans-* and 34% *cis,trans-* pyrrolidines (the mixture resulting from Example 1C), 220 mg of diisopropylethylamine and 185 mg of 4-fluorobenzyl bromide were reacted at room temperature for 3 hours in 1 mL of acetonitrile to give 387 mg of a mixture of *trans,trans-* and *cis,trans-*N-alkylated esters. A portion (360 mg) was hydrolyzed with 250 mg NaOH in 1 mL of water and 4 mL of ethanol to give 160 mg of the title compound as an amorphous powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.74 (t, J = 9 Hz, 1H), 2.95 (t, J = 7 Hz, 1H), 2.98 (d, J = 14, 1H), 3.07 (dd, J = 9 Hz, 1 Hz, 1H), 3.42-3.53 (m, 1H), 3.70 (d, J = 9 Hz, 1H), 3.78 (d, J = 14, 1H), 3.81 (s, 3H), 5.92 (s, 2H), 6.70 (d, J = 8 Hz, 1H), 6.77 (dd, J = 8 Hz, 1 Hz, 1H), 6.91 (d, J = 9 Hz, 2H), 6.94 -7.00 (m, 3H), 7.20 - 7.25 (M, 1H), 7.44 (d, J = 9 Hz, 2H).

Example 4

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-ethoxyethyl)-pyrrolidine-3-carboxylic acid

Using the method described in Example 1D, 300 mg. of the mixture of 64% *trans,trans-* and 34% *cis,trans-*pyrrolidines (the mixture resulting from Example 1C), 220 mg of diisopropylethylamine and 152 mg of 2-bromoethyl ethyl ether were refluxed in 1.5 mL acetonitrile for 3 hours (bath temperature at 95 °C) to give 346 mg of a mixture of *trans,trans-* and *cis,trans-*esters. Hydrolysis with 250 mg NaOH in 1 mL of water and 3 mL of ethanol afforded 140 mg of the title compound. m.p. 88 - 90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J = 7 Hz, 3H), 2.21-2.32 (m, 1H), 2.70-2.80 (m, 1H), 2.85-2,94 (m, 2H), 3.38-3.55 (m, 6H), 3.67 (d, J = 10 Hz, 1H), 3.79 (s, 3H), 5.94 (s, 2H), 6.72 (d, J = 8 Hz, 1H), 6.84 (m, 1H), 6.84 (d, J = 9 Hz, 2H), 7.08 (d, J = 1 Hz, 1H), 7.33 (d, J = 9 Hz, 2H).

Example 5

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-propoxyethyl)-pyrrolidine-3-carboxylic acid

Using the method described in Example 1D, 520 mg of the mixture resulting from Example 1C, 364 mg of diisopropylethylamine, 50 mg potassium iodide and 350 mg 2-chloroethyl propyl ether were reacted at 125 °C in 0.5 mL acetonitrile for 4 hours to give 517 mg of a mixture of *trans,trans-* and *cis,trans-*esters. A portion (500 mg) was hydrolyzed with 315 mg NaOH in 1 mL of water and 4 mL of ethanol to give 225 mg of the title compound as an amorphous powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 7 Hz, 3H), 1.53 (sextet, J = 7 Hz, 2H), 2.28-2.41 (m, 1H), 2.71-2.83 (m, 1H), 2.92-3.08 (m, 2H), 3.30 (t, J = 7 Hz, 2H), 3.40-3.60 (m, 4H), 3.72-3.83 (m, 1H), 3.76 (s, 3H), 5.92 (s, 2H), 6.71 (d, J = 8 Hz, 2H), 6.74 (dd, J = 8 Hz, 1 Hz), 6.71 (d, J = 9 Hz, 2H), 7.07 (d, J = 9 Hz, 2H), 7.73 (d, J = 9 Hz, 2H).

Example 6

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(2-methoxyethoxy)ethyl]-pyrrolidine-3-carboxylic acid

Example 6A

Ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl) pyrrolidine-3-carboxylate

To the pure *cis,cis*-compound resulting from Example 1C (3.02 g) dissolved in 10 mL of ethanol was added 20 drops of a solution of 21% sodium ethoxide in ethanol. The reaction mixture was refluxed overnight, at which time thin layer chromatography in ethyl acetate indicated the absence of starting material. The NaOEt was neutralized with HCl in ethanol, and the solution was concentrated *in vacuo*. The residue was taken up in toluene and extracted with potassium bicarbonate in water. The toluene was dried over sodium sulfate and concentrated under reduced pressure to give 2.775 of the title compound which was pure by TLC (ethyl acetate).

Example 6B

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(2-methoxyethoxy)ethyl]-pyrrolidine-3-carboxylic acid

Using the method described in Example 1D, 250 mg of the compound resulting from Example 6A, 150 mg of 2-(2-methoxyethoxy)ethyl bromide and 175 mg diisopropyl-ethylamine in 1 mL acetonitrile were heated at 100 °C for 3 hours to give 229 mg of the *trans,trans*-ester. A portion (200 mg) was hydrolyzed with 125 mg NaOH in 1 mL of water and 2 mL of ethanol to give 151 mg of the title compound as an amorphous powder. ^{1}H NMR (CD_3OD, 300 MHz) δ 2.9-3.9 (m, 13H), 3.81 (s, 3H), 4.49 (d, J = 10 Hz, 1H), 5.94 (s, 2H), 6.79 (d, J = 8 Hz, 1H), 6.89 (dd, J = 8 Hz, 1 Hz, 1H), 7.00 (d, J = 9 Hz, 2H), 7.05 (d, J = 1 Hz, 1H), 7.49 (d, J = 9 Hz, 2H).

Example 7

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(2-pyridyl)ethyl]-pyrrolidine-3-carboxylic acid

The compound resulting from Example 6A (250 mg), 2-vinyl pyridine (355 mg) and one drop of acetic acid were dissolved in 2-methoxyethanol, and stirred at 100 °C for 2.5 hours. Toluene was added, and the solution was washed with potassium bicarbonate solution. The solution was dried over potassium bicarbonate and concentrated *in vacuo*. Toluene was added and the solution re-concentrated. This was done until the odor of 2-vinylpyridine was gone. The residue was taken up in hot heptane, filtered to remove a small amount of insoluble

impurity, and concentrated *in vacuo* to give 225 mg of intermediate ester. The ester was hydrolyzed by the method described in Example 1D to give 202 mg of the title compound as the dihydrate. m.p. 77-80 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 2.8 - 3.3 (m, 6H), 3.55-3.70 (m, 2H), 3.76 (s, 3H), 3.99 (d, J = 10 Hz, 1H), 5.92 (d, J = 1 Hz, 2H), 6.72 (d, J = 8 Hz, 1H), 6.80 (dd, J = 8 Hz, 1 Hz), 6.85 (d, J = 9 Hz, 2H), 6.92 (d, J = 1 Hz, 1H), 7.20 (d, J = 9 Hz, 2H), 7.20-7.32 (m, 2H), 7.70-7.80 (m, 2H), 8.40 (d, J = 4 Hz, 1H).

Example 8

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(morpholin-4-ylcarbonyl)-pyrrolidine-3-carboxylic acid

To the compound resulting from Example 6A (300 mg) and 164 mg triethylamine dissolved in 2 mL of methylene chloride and cooled in an ice bath was added 146 mg 1-morpholinocarbonyl chloride. The mixture was stirred 3 hours at room temperature. Toluene was added and the solution was washed with potassium bicarbonate solution, dried over sodium sulfate and concentrated *in vacuo* to give the intermediate ester. The ester was hydrolyzed by the method described in Example 1D to give 288 mg of the title compound. m.p. 244-246 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.96 (dd, J = 12,Hz, 13 Hz, 1H), 3.03-3.13 (m, 2H), 3.20-3.30 (m, 2H), 3.40-3.60 (m, 5H), 3.74 (s, 3H), 3.70-3.85 (m, 3H), 5.10 (d, J = 10 Hz, 1H), 5.99 (d, J = 1 Hz, 2H), 6.80-6.90 (m, 2H), 6.87 (d, J = 9 Hz, 2H), 7.07 (s, 1H), 7.25 (d, J = 9 Hz, 2H).

Example 9

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxole-5-yl)-1-(butylaminocarbonyl)-pyrrolidine-3-carboxylic acid

To the compound resulting from Example 6A (300 mg) dissolved in 2 mL tetrahydrofuran and cooled in an ice bath was added 88 mg of butyl isocyanate. After 40 minutes at room temperature, toluene was added, and the solution was concentrated *in vacuo* to give the intermediate ester. The ester was hydrolyzed by the method described in Example 1D to give 232 mg of the title compound. m.p. 220-221 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.78 (t, J = 7 Hz, 3H), 1.10 (sextet, J = 7 Hz, 2H), 1.22 (quintet, J = 7 Hz, 2H), 2.78-3.05 (m, 3H), 3.40-3.56 (m, 2H), 3.74 (s, 3H), 3.95-4.05 (m, 1H), 4.93 (d, J = 9 Hz, 1H), 5.80 (t, broad, J = 7 Hz, 1H), 5.99 (s, 2H), 6.78-6.86 (m, 2H), 6.88 (d, J = 9 Hz, 2H), 7.00 (d, J = 1 Hz, 1H), 7.12 (d, J = 9 Hz, 2H).

Example 10

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(4-methoxyphenylaminocarbonyl)-3-pyrrolidine-3-carboxylic acid

The compound resulting from Example 6A (300 mg) was treated with 133 mg of 4-methoxyphenyl isocyanate by the procedure described in Example 9. The resulting ester was hydrolyzed with NaOH using the method described in Example 1D to give 279 mg of the title compound. m.p. 185-187 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.23 (dd, J = 12 Hz, 13 Hz, 1H), 3.55-3.68 (m, 2H), 3.72 (s, 3H), 3.83 (s, 3H), 4.50-4.65 (m, 1H), 5.06 (d, J = 10 Hz, 1H), 5.90 (s, 1H), 5.95 (s, 1H), 6.72 (d, J = 9 Hz, 2H), 6.7-6.8 (m, 3H), 6.92 (d, J = 9 Hz, 2H), 6.97 (d, J = 9 Hz, 2H), 7.37 (d, J = 9 Hz, 2H).

Example 11

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-acetylpyrrolidine-3-carboxylic acid

The compound resulting from Example 6A (250 mg) in 0.5 mL of toluene was treated with 200 mg of acetic anhydride. After stirring 2 hours at room temperature, water was added and the acetic acid neutralized with potassium bicarbonate. The mixture was extracted with toluene to give 273 mg of the intermediate ester. A portion of the ester (200 mg) was hydrolyzed using the method of Example 1D to give 211 mg of the title compound. m.p. 248-250 °C. Rotational isomers are seen in the NMR. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.55 and 2.00 (s, 3H), 2.94 and 3.03 (dd, J = 12 Hz, 13 Hz, 1H), 3.3-3.6 (m, 2H), 3.72 and 3.76 (s, 3H), 4.12 and 4.28 (dd, J = 12 Hz, 7 Hz, 1H), 4.95 and 5.04 (d, J = 10Hz, 1H), 6.00 (s, 2H), 6.75-6.87 (m, 3H), 6.95 and 7.04 (d, J = 9 Hz, 2H), 7.18 and 7.32 (d, J = 9 Hz, 2H).

Example 12

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-furoyl)-pyrrolidine-3-carboxylic acid

To the compound resulting from Example 6A (300 mg) and 164 mg triethylamine dissolved in 2 mL methylene chloride and cooled in an ice bath was added 138 mg of 2-furoyl chloride. The mixture was stirred 30 minutes at room temperature and then worked up by the procedures described in Example 8 to give the intermediare ester. The ester was hydrolyzed by the procedure described in Example 1D to give 269 mg of the title compound as an amorphous powder. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.06 (dd, J = 12 Hz, 13 Hz, 1H), 3.3-3.6 (m, 2H), 4.25 (m, 1H), 5.19 (d, J = 10 Hz, 1H), 6.67.4 (m, 8H), 7.8-7.9 (m, 1H).

Example 13

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(phenylaminocarbonyl)-pyrrolidine-3-carboxylic acid

Starting with the compound resulting from Example 6A, phenyl isocyanate and the procedures described in Example 9, the title compound was prepared. m.p. 209-211 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.03 (dd, 1H), 3.55 (m, 1H), 3.70 (m, 1H), 3.72 (s, 3H), 4.15 (m, 1H), 5.13 (d, 1H), 6.00 (s, 2H), 6.88 (m, 5H), 7.07-7.20 (m, 3H), 7.30 (d, 2H), 7.38 (d, 2H), 8.20 (bs, 1H).

Example 14

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(allylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared. m.p. 138-140 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.84 (d, 1H), 2.90-3.10 (dt, 2H), 3.28 (d, 1H), 3.35 (dd, 1H), 3.62 (m, 1H), 3.72-3.97 (m, 3H), 3.80 (s, 3H), 5.13 (bd, 2H), 5.80 (m, 1H), 5.97 (s, 2H), 6.74-6.97 (m, 5H), 7.38 (d, 2H).

Example 15

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(n-butylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared. m.p. 105-107 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H), 1.30 (m, 2H), 1.45 (m, 2H), 2.80 (d, 1H), 2.87-3.35 (m, 6H), 3.62 (m, 1H), 3.80 (s, 3H), 5.97 (s, 2H), 6.75-6.92 (m, 5H), 7.28 (d, 2H).

Example 16

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(n-propyl)-N-methylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared as an amorphous solid. Rotational isomers are seen in the NMR. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73, 0.84 (2t, 3H), 1.49 (m, 2H), 2.80 (dd, 1H), 2.85 (2s, 3H), 2.95-3.20 (m, 3H), 3.20-3.40 (m, 1H), 3.40 (d, 1H), 3.60 (m, 1H), 3.79 (s, 3H), 5.93 (s, 2H), 6.73 (d, 1H), 6.86 (m, 2H), 7.03 (m, 1H), 7.32 (d, 2H).

Example 17

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(pyrrolidin-1-ylcarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared as an amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40-1.70 (m, 6H), 2.80 (d, 1H), 3.00 (m, 2H), 3.24-3.43 (m, 5H), 3.60 (m, 2H), 3.73 (d, 1H), 3.80 (s, 3H), 5.95 (s, 2H), 6.74 (d, 1H), 6.80-6.90 (m, 3H), 7.04 (d, 1H), 7.30 (d, 2H).

Example 18

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(isobutylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared. m.p. 175-177 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.87 (dd, 6H), 1.75 (septet, 1H), 2.85 (d, 1H), 2.90-3.10 (m, 4H), 3.23 (d, 1H), 3.40 (m, 1H), 3.58-3.67 (m, 1H), 3.78 (s, 3H), 3.89 (d, 1H), 5.92 (s, 2H), 6.76 (d, 1H), 6.86 (dd, 1H), 6.91 (d, 2H), 7.02 (d, 1H), 7.40 (d, 2H).

Example 19

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(cyclopentylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared. m.p. 137-139 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (m, 2H), 1.62 (m, 4H), 1.90 (m, 2H), 2.76 (d, 1H), 2.90 (t, 1H), 3.04 (dd, 1H), 3.22 (d, 1H), 3.28 (dd, 1H), 3.40 (m, 1H), 3.80 (s, 3H), 4.15 (m, 1H), 5.97 (d, 2H), 6.75-6.95 (m, 5H), 7.27 (m, 2H).

Example 20

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(morpholin-4-ylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared as an amorphous solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.82 (d, 1H), 3.00 (m, 2H), 3.24 (m, 1H), 3.30-3.52 (m, 4H), 3.52-3.75 (m, 8H), 3.80 (s, 3H), 5.95 (s, 2H), 6.75 (d, 1H), 6.84 (d, 3H), 7.00 (s, 1H), 7.28 (d, 2H).

Example 21

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-phenoxyethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 4 the title compound was prepared as an amorphous solid. ^{1}H NMR (CD_3OD, 300 MHz) δ 2.82 (m, 1H), 2.96 (dd, 1H), 3.13 (m, 1H), 3.32 (m, 1H), 3.51-3.70 (m, 2H), 3.77 (s, 3H), 4.00 (d, 1H), 4.07 (m, 2H), 5.91 (s, 2H), 6.72 (d, 1H), 6.80-6.95 (m, 6H), 7.03 (d, 1H), 7.22 (dd, 2H), 7.39 (d, 2H).

Example 22

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-methoxyethylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared. m.p. 107-109 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 2.82 (d, 1H), 2.97 (q, 2H), 3.21 (d, 1H), 3.38 (m, 1H), 3.32 (s, 3H), 3.44 (m, 4H), 3.62 (m, 1H), 3.79 (s, 3H), 3.86 (d, 1H), 5.93 (s, 2H), 6.76 (d, 1H), 6.85 (dd, 1H), 6.91 (d, 2H), 7.01 (d, 1H), 7.38 (d, 2H).

Example 23

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-butoxyethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 4 the title compound was prepared. m.p. 53-55 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J=7Hz, 3H), 1.32 (sextet, J=7Hz, 2H), 1.50 (pentet, J=7Hz, 2H), 2.27 (tt, J=6Hz, 6Hz, 1H), 2.92 (q, J=10Hz, 2H), 3.35 (t, J=7Hz, 2H), 3.42-3.56 (m, 4H), 3.68 (d, J=10Hz, 1H), 3.78 (s, 3H), 5.94 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.83 (d, J=9Hz, 2H), 6.82-6.87 (m, 1H), 7.06 (d, J=2Hz, 1H), 7.32 (d, J=9Hz, 2H). MS m/e 442 $(M+H)^+$.

Example 24

trans,trans-2-(1,3-Benzodioxol-5-yl)-4-(4-methoxyphenyl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 and substituting ethyl (1,3-benzodioxol-5-ylcarbonyl)acetate for ethyl (4-methoxybenzoyl)acetate and 4-(2-nitrovinyl)anisole for 5-(2-nitrovinyl)-1,3-benzodioxol-5yl afforded the title compound. m.p. 97-99 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J=7Hz, 3H), 1.39 (sextet, J=7Hz, 2H), 2.72 (d, J=16Hz, 1H), 2.74 (t, J=10Hz, 1H), 2.80-3.10 (m, 4H), 3.26-3.38 (m, 1H), 3.53 (m, 1H), 3.73 (s, 3H), 3.80 (d, J=10Hz, 2H), 7.80 (t, J=6Hz, 1H). MS (DCI/NH_3) m/e 441 $(M+H)^+$.

Example 25

trans,trans-2-(1,3-Benzodioxol-5-yl)-4-(4-methoxyphenyl)-1-(2-propoxyethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 5 and substituting ethyl (1,3-benzodioxol-5-ylcarbonyl)acetate for ethyl (4-methoxybenzoyl)acetate and 4-(2-nitrovinyl)anisole for 5-(2-nitrovinyl)-1,3-benzodioxol-5yl afforded the title compound. m.p. 67-69 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J=7Hz, 3H), 1.56 (sextet, J=7Hz, 2H), 2.33 (m, 1H), 2.78-3.00 (m, 3H), 3.32 (t, J=7Hz, 2H), 3.45-3.57 (m, 4H), 3.73 (m, 1H), 3.79 (s, 3H), 5.93 (s, 2H), 6.22 (d, J=8Hz, 1H), 6.85 (d, J=8Hz, 3H), 6.98 (s, 1H), 7.37 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 428 $(M+H)^+$.

Example 26

trans,trans-2-(1,3-Benzodioxol-5-yl)-4-(4-methoxyphenyl)-1-[2-(2-methoxyethoxy)ethyl)]-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 4 and substituting the starting materials described in Example 25 and using 2-(2-methoxyethoxy)ethylbromide to alkylate the pyrrolidine nitrogen afforded the title compound. m.p. 85-86 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 3.18-3.90 (m, 15H), 3.79 (s, 3H), 4.57 (d, J=10Hz, 1H), 6.02 (s, 2H), 6.91 (d, J=8Hz, 1H), 6.95 (d, J=9Hz, 2H), 7.06 (dd, J=8Hz, 1H), 7.12 (dd, J=1Hz, 1H), 7.37 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 444 $(M+H)^+$.

Example 27

trans,trans-2-(1,3-Benzodioxol-5-yl)-4-(4-methoxyphenyl)-1-(butoxyethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 4, substituting the starting materials described in Example 25 and using 2-ethoxyethylbromide to alkylate the pyrrolidine nitrogen afforded the title compound. m.p. 54-56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J-7Hz,

3H), 1.44 (sextet, J=7Hz, 2H), 1.52 (pentet, J=7Hz, 2H), 2.40 (m, 1H), 2.74-2.98 (m, 3H), 3.46 (t, J=7Hz, 2H), 3.42-3.56 (m, 4H), 3.68 (d, J=10Hz, 1H), 3.80 (s, 3H), 5.93 (dd, J=6Hz, 1Hz, 2H), 6.72 (d, J=8Hz, 1H), 6.74 (dd, J=9Hz, 3H), 6.96 (s, 1H), 7.36 (d, J=9Hz, 2H).

Example 28

trans,trans-2-(4-Methoxyphenyl)-4-(1,4-benzodioxan-6-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 and substituting 6-(2-nitrovinyl)-1,4-benzodioxane for 5-(2-nitrovinyl)-1,3-benzodioxole afforded the title compound. m.p. 80-81 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J-7Hz, 3H), 1.49 (sextet, J=7Hz, 2H), 2.78 (d, J=16Hz, 1H), 2.92 (t, J=10Hz, 1H), 3.05-3.43 (m, 5H), 3.24 (d, J=16Hz, 1H), 3.52-3.62 (m, 1H), 3.80 (s, 3H), 3.80 (t, J=10Hz, 1H), 4.27 (s, 4H), 6.74-6.93 (m, 5H), 7.29 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 455 $(M+H)^+$.

Example 29

trans,trans-2-(4-Methoxyphenyl)-4-(1,4-benzodioxan-6-yl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, substituting 6-(2-nitrovinyl)-1,4-benzodioxane for 5-(2-nitrovinyl)-1,3-benzodioxole and alkylating the pyrrolidine nitrogen with N-methyl-N-propyl bromoacetamide afforded the title compound. m.p. 74-76 °C. Rotational isomers are seen in the NMR. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73, 0.83 (2t, J=7Hz, 3H), 1.48 (m, 2H), 2.78 (dd, 1H), 2.85 (2s, 3H), 2.96-3.15 (m, 3H), 3.27-3.42 (m, 3H), 3.52-3.60 (m, 1H), 3.75 (d, 1H), 3.78 (s, 3H), 4.22 (s, 4H), 6.80-6.98 (m, 5H), 7.32 (d, 2H). MS (DCI/NH_3) m/e 469 $(M+H)^+$.

Example 30

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-butylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. Rotational isomers are seen in the NMR. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.86 (2t, 3H), 1.04-1.50 (m, 4H), 2.85 (2s, 3H), 2.93-3.20 (m, 4H), 3.40 (m, 2H), 3.52 (dd, 1H), 3.60 (m, 1H), 3.80 (s, 3H), 3.85 (m, 1H), 5.91 (s, 2H), 6.74 (d, 1H), 6.83-6.95 (m, 3H), 7.03 (dd, 1H), 7.35 (dd, 2H).

Example 31

trans,trans-2-(4-Methoxy-2-methoxymethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-butylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 31A

Ethyl 2-(4-methoxy-2-methoxymethoxyphenyl-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate)

Using the procedures described in Examples 1A and 1B and substituting ethyl (4-methoxy-2-methoxymethoxybenzoyl)acetate for ethyl (4-methoxybenzoyl)acetate afforded ethyl 2-(4-methoxy-2-methoxymethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-4,5-dihydro-3H-pyrrole-3-carboxylate.

The above dihydro pyrrole carboxylate (3.0 g, 7.0 mmol) was dissolved in 20 mL of methanol, treated with 500 mg of 10% Pd/C and placed under hydrogen atmosphere for 32 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure and chromatographed on silica gel eluting with ethyl acetate to afford the title compound (1.9 g, 63%) as the *cis-cis* isomer.

Example 31B

trans,trans-2-(4-Methoxy-2-methoxymethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-butylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound resulting from Example 31A was epimerized by the procedure described in Example 6A. The resulting *trans,trans* compound (100 mg, 0.23 mmol) was then reacted by the procedures described in Example 1D substituting N-methyl-N-butyl bromoacetamide for N-propyl bromoacetamide to give the title compound (75 mg, 62%). m.p. 65-67 °C. Rotational isomers are seen in the NMR. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.64, 0.68 (2t, J=7Hz, 3H), 1.14, 1.12 (2 sextet, J=7Hz, 2H), 1.40-1.48 (m, 2H), 2.86, 2.89 (2s, 3H), 2.95-3.42 (m, 6H), 3.50 (s, 3H), 3.43-3.65 (m, 2H), 3.78 (s, 3H), 4.30 (t, J=7Hz, 1H), 5.09 (q, J=7Hz, 2H), 5.92 (s, 2H), 6.55 (dd, J=3Hz, 1H), 6.68 (s, 1H), 6.72 (s, 1H), 6.85 (2t, J=1Hz, 1H), 7.04 (t, J=1Hz, 1H), 7.42 (dd, J=3Hz, 1H).

Example 32

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3-ethoxypropyl)-pyrrolidin-5-one-3-carboxylic acid

Example 32A

Ethyl 2-(4-methoxybenzoyl)-3-carbomethoxy-1,3-benzodioxole-5-propionate

To ethyl (4-methoxybenzoyl)acetate (4.44 g, 0.02 mmol) dissolved in 20 mL of anhydrous THF was added in portions 480 mg of NaH. The mixture was stirred for 30 minutes under nitrogen at ambient temperature. Methyl (1,3-benzodioxol-5-yl) bromoacetate (5.46 g, 0.02 mol) in 5 mL of THF was added. The mixture was stirred overnight at ambient

temperature, diluted with 200 mL of EtOAc, and washed with water and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound (7.67 g, 92%) which was used without further purification.

Example 32B
Ethyl 1-(3-ethoxypropyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-4,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate

A mixture of the compound resulting from Example 32A (700 mg, 1.69 mmol), 3-ethoxypropylamine (348 mg, 3.38 mmol) and 1 mL of acetic acid in a sealed tube was heated for 18 hours at 125 °C. After cooling the contents of the tube to ambient temperature, 5 mL of water was added and the mixture extracted with ethyl acetate (2x100 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution, water and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 3:2 hexane-ethyl acetate to give 330 mg (42%) of the title compound.

Example 32C
Ethyl 1-(3-ethoxypropyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidin-5-one-3-carboxylate

The compound resulting from Example 32B (300 mg, 0.64 mmol) in 15 mL of methanol was reduced with 100 mg of 10% Pd/C under hydrogen for 3 hours at ambient temperature. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give the title compound.

Example 32D
trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3-ethoxypropyl)-pyrrolidin-5-one-3-carboxylic acid

To the compound resulting from Example 32C (100 mg, 0.21 mmol) dissolved in 1 mL of ethanol was added 3 drops of a solution of 21% sodium ethoxide in ethanol. The mixture was heated to 70-80 °C for 3 hours, and then a solution of sodium hydroxide (100 mg) in 1 mL of water was added and heating was continued for 1 additional hour. The reaction mixture was cooled to ambient temperature, the ethanol was removed under reduced pressure, and water was added to the residue which was washed with ether. The aqueous layer was neutralized with 3 M HCl and allowed to stand overnight. The white crystalline solid was collected by filtration to give the title compound (60 mg, 64%). m.p. 134-140 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.04 (t, J=7Hz, 3H), 1.55 (sextet, J=7Hz, 2H), 2.48-2.56 (m, 1H), 2.93 (dd, J=9Hz, 1H), 3.25 (t, J=7Hz, 2H), 3.28-3.40 (m, 2H), 3.48-3.57 (m, 1H),

3.78 (s, 3H), 3.88 (d, J=10Hz, 1H), 4.72 (d, J=10Hz, 1H), 6.02 (s, 2H), 6.74 (dd, J=8Hz, 1Hz, 1H), 6.87 (d, J=8Hz, 2H), 6.98 (d, J=8Hz, 2H), 7.38 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 442 $(M+H)^+$.

Example 33

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3-methoxybenzyl)-pyrrolidin-5-one-3-carboxylic acid

Following the procedures described in Example 32 and substituting 3-methoxybenzylamine for 3-ethoxypropylamine afforded the title compound (123 mg, 65%). m.p. 150-152 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 2.96 (dd, J=8Hz, 10Hz, 1H), 3.72 (s, 3H), 3.80 (s, 3H), 4.06 (d, J=10Hz, 1H), 4.58 (d, J=8Hz, 1H), 4.92 (q, J=16Hz, 2H), 5.92 (s, 2H), 6.55-6.63 (m, 2H), 6.82 (d, J=8Hz, 4H), 6.94 (d, J=8Hz, 2H), 7.15-7.22 (m, 3H). MS (DCI/NH_3) m/e 475 $(M+H)^+$.

Example 34

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-diisoamylaminocarbonylmethyl)-pyrrolidine-3carboxylic acid

The title compound was prepared as an amorphous solid using the procedures described in Example 1. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 -0.90 (m, 12H), 1.10-1.60 (m, 10H), 2.75 (d, J=13Hz, 1H), 2.90-3.10 (m, 4H), 3.15 - 3.30 (m, 2H), 3.40 (d, J=10Hz, 1H), 3.40 - 3.52 (m, 2H), 3.55 - 3.62 (m, 1H), 3.75 (d, J=12 Hz, 1H), 3.79 (s, 3H), 5.93 (dd, J =1 Hz, 3 Hz, 2H), 6.72 (d, J=8Hz, 1H), 6.82-6.90 (m, 3H), 7.03 (d, J=2Hz, 1H), 7.30 (d, J=9Hz, 2H).

Example 35

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-dipentylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared as an amorphous solid using the procedures described in Example 1. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J = 7Hz, 6H), 0.95-1.03 (m, 2H), 1.10-1.30 (m, 8H), 1.40-1.51 (m, 2H), 2.72 (d, J=13Hz, 1H), 2.90-3.08 (m, 4H), 3.25-3.50 (m, 3H), 3.37 (d, J=13Hz, 1H), 3.52-3,60 (m, 1H), 3.70 (J=10Hz, 1H), 3.75 (s, 3H), 5.92 (dd, J=2Hz, 5Hz, 2H), 6.72 (d, J=8Hz, 1H), 6.80-6.88 (m, 3H), 7.03 (d, J=2Hz, 1H), 7.30 (d, J=9Hz, 2H).

Example 36

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(2-methoxyethyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared using the procedures described in Example 1. m.p. 120-122 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.82 (d, J=13, 1H), 2.94-3.08 (m, 2H), 3.12 (s, 3H), 3.23 (s, 3H), 3.20-3.70 (m, 11H), 3.73 (d, J=10Hz, 1H), 3.79 (s, 3H), 5.92 (dd, J= 2Hz, 2Hz, 2H), 6.72 (d, J=8Hz, 1H), 6.80-6.90 (m, 3H), 7.04 (d, J=2Hz, 1H), 7.30 (d, J=9Hz, 2H).

Example 37

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-hexynyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 4, 200 mg. of the pure *trans,trans* isomer, the compound resulting from Example 6A was reacted with 109 mg of 1-bromo-2-hexyne, prepared by the method described in Perkin I, , 2004 (1987), for 1 hour at 55 °C, to give 226 mg of the intermediate ester. The ester was hydrolyzed using NaOH in ethanol-water for 3 hours at room temperature to give 175 mg of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, J=7Hz, 3H), 1.54 (m, 2H), 2.14-2.22 (m, 2H), 2.96 (dd, J=7Hz, 13Hz, 1H), 3.07 (dd, J=18Hz, 2Hz, 1H), 3.15 (dd, J=9Hz, 2Hz, 1H), 3.26 (t, J=9Hz, 1H), 3.36 (dd, J = 18 Hz, 2Hz, 1H), 3.47-3.55 (m, 1H), 3.79 (s, 3H), 3.88 (d, J=9Hz, 1H), 5.95 (s, 2H), 6.72 (d, J=8Hz, 1H), 6.80-6.88 (m, 3H), 7.03 (d, J=2Hz, 1H), 7.22 (d, J=9Hz, 2H).

Example 38

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-cyclopropylmethyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared using the procedures described in Example 1. m.p. 167-169 °C. Rotational isomers were seen in the NMR. ^{1}H NMR ($CDCl_3$, 300 MHz) δ -0.1 (m), 0.05 (m), 0.12-0.25 (m), 0.32-0.51 (m), 0.67 and 0.74 (2 triplets, 3H), 0.90-1.00 (m), 1.20-1.55 (m), 2.72 (d, J=13Hz, 1H), 2.85--3.29 (m, 4H), 3.30-3.50 (m, 3H), 3.52-3.62 (m, 1H), 3.65-3.73 (2 doublets, J=10Hz, 2Hz, 1H), 3.78 (s, 3H), 5.95 (2 singlets, 2H), 6.72 (2 doublets, 2H), 6.80-6.90 (m, 3H), 7.00 and 7.05 (2 doublets, J=9Hz, 2H).

Example 39

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-pentylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared as an amorphous solid using the procedures described in Example 1. Rotational isomers were seen in the NMR. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J=7Hz, 3H), 1.00-1.08 (m), 1.13-1.32 (m), 1.35-1,50 (m), 2.72-2.82 (2

doublets, J=13Hz, 1H), 2.83 and 2.86 (2 singlets, 3H), 2.92-3.20 (m, 3H), 3.22-3.45 (m, 3H), 3.52-3.62 (m, 1H), 3.72 (2 doublets, 1H), 3.75 and 3.76 (2 singlets, 3H), 5.92 (2 singlets, 2H), 6.72 (d, J=8Hz, 1H), 6.80-6.87 (m, 3H), 7.03 (2 doublets, J=2Hz, 1H), 7.30 (d, J=9Hz, 2H).

Example 40

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-diisobutylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared using the procedures described in Example 1. m.p. 141-143 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.54 (d, J=7Hz, 3H), 0.70-0.90 (3 doublets, J=7Hz, 9H), 1.60-1.75 (m, 1H), 1.90-2.02 (m, 1H), 2.67 (d, J=13Hz, 1H), 2.70 (d, J=13Hz, 1H), 2.84 (dd, J=6Hz, 15Hz, 1H), 2.96-3.06 (m, 2H), 3.20 (dd, J=9Hz, 15Hz, 1H), 3.35 (dd, J=2Hz, 10Hz, 1H), 3.44-3.60 (m, 4H), 3.70 (d, J=9Hz, 1H), 3.79 (s, 3H), 5.94 (dd, J=2Hz, 2Hz, 2H), 6.72 (d, J=9Hz, 1H), 6.82-6.90 (m, 3H), 7.03 (d, J=2Hz, 1H), 7.31 (d, J=9Hz, 2H).

Example 41

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-(2-propynyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared as an amorphous solid using the procedures described in Example 1. Rotational isomers were seen in the NMR. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.09 and 2.32 (2 triplets, J=2Hz, 1H), 2.80-3.10 (m, 3H), 2.90 and 2.99 (2 singlets, 3H), 3.35-3.50 (m, 2H), 3.52-3.62 (m, 1H), 3.78 (s, 3H), 4.03 (d, J=13Hz, 1H), 4.00-4.30 (m, 3H), 5.93 (s, 2H), 6.72 (2 doublets, J=8Hz, 1H), 6.80-6.90 (m, 3H), 7.02 and 7.11 (2 doublets, J = 2Hz, 1H), 7.30 (2 doublets, J=9Hz, 2H).

Example 42

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-(n-hexyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared as an amorphous solid using the procedures described in Example 1. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (2 triplets, J=7Hz, 3H), 1.00-1.50 (m, 8H), 2.72-2.82 (2 doublets, J=13Hz, 1H), 2.81 and 2.86 (2 singlets, 3H), 2.92-3.20 (m, 3H), 3.22-3.45 (m, 3H), 3.52-3.62 (m, 1H), 3.72 (2 doublets, 1H), 3.75 and 3.76 (2 singlets 3H), 5.94 (2 singlets, 2H), 6.72 (d, J=8Hz, 1H), 6.80-6.87 (m, 3H), 7.03 (2 doublets, J=2Hz, 1H), 7.30 (d, J=9Hz, 1H).

Example 43

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-*(N,N-di(n-butyl)aminocarbonylmethyl)*-pyrrolidine-3-carboxylic acid

The title compound was prepared using the procedures described in Example 1. m.p. 123-125 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J=7Hz, 3H), 0.85 (t, J=7Hz, 3H), 1.00-1.50 (m, 8H), 2.74 (d, J=13Hz, 1H), 2.90-3.09 (m, 4H), 3.23-3.50 (m, 3H), 3.38 (d, J=13Hz, 1H), 3.52-3.62 (m, 1H), 3.75 (d, J=10 Hz, 1H), 3.78 (s, 3H), 5.93 (dd, J=2Hz, 4Hz), 6.71 (d, J=8Hz, 1H), 6.81-6.89 (m, 3H), 7.03 (d, J=2Hz, 1H), 7.30 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/e 511 $(M+H)^+$. Anal calcd for $C_{29}H_{38}N_2O_6$: C, 68.21; H, 7.50; N, 5.49. Found: C, 68.07; H, 7.47; N, 5.40.

Example 44

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-diethylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared using the procedures described in Example 1. m.p. 132-134 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, J=7Hz, 3H), 1.06 (t, J=7Hz, 3H), 2.78 (d, J=13 Hz, 1H), 2.95-3.20 (m, 4H), 3.30-3.50 (m, 4H), 3.55-3.65 (m, 1H), 3.76 (d, J=12 Hz, 1H), 3.79 (s, 3H), 5.93 (s, 2H), 6.72 (d, J=8Hz, 1H), 6.80-6.90 (m, 3H), 7.02 (d, J=2Hz, 1H), 7.32 (d, J=9Hz, 2H).

Example 45

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared as an amorphous solid using the procedures described in Example 1. ^{1}H NMR (CD_3OD, 300 MHz) δ 2.75-2.85 (m, 2H), 3.05-3.13 (m, 1H), 3.18 (s, 3H), 3.40-3.58 (m, 2H), 3.78 (s, 3H), 3.88 (d, J=12Hz, 1H), 5.92 (s, 2H), 6.72 (d, J=8Hz, 1H), 6.75-6.85 (m, 3H), 7.00-7.12 (m, 5H), 7.82-7.92 (m, 3H).

Example 46

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-cyclohexylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared as an amorphous solid using the procedures described in Example 1. Rotational isomers were seen in the NMR. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.00-1.85 (m, 10H), 2.72 and 2.78 (2 singlets, 3H), 2.75-2.82 (2 doublets, J=12Hz, 1H), 2.96-3.22 (m, 3H), 3.40-3.65 (m, 3H), 3.68 and 3.82 (2 doublets, J=10Hz, 1H), 3.77 and 3.78 (2 singlets, 3H), 5.92 (s, 2H), 6.72 (2 doublets, J=8Hz, 1H), 6.82-6.88 (m, 3H), 7.02 (2 doublets, J=2Hz, 1H), 7.30-7.40 (2 doublets, J=9Hz, 2H).

Example 47

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-propyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared using the procedures described in Example 1. m.p. 170-172 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.69 (t, J=7Hz, 3H), 0.85 (t, J=7Hz, 3H), 1.20-1.55 (m, 4H), 2.72 (d, J=13Hz, 1H), 2.90-3.10 (m, 4H), 3.25-3.47 (m, 4H), 3.35-3.62 (m, 1H), 3.72 (d, J=9Hz, 1H), 3.79 (s, 3H), 5.94 (s, 2H), 6.72 (d, d, J=8Hz, 1H), 6.80-6.90 (m, 3H), 7.02 (d, J=2Hz, 1H), 7.30 (d, J=9Hz, 2H).

Example 48

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-isobutylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared as an amorphous solid using the procedures described in Example 1. Rotational isomers were seen in the NMR. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.65-0.85 (4 doublets, J=7Hz, 6H), 1.75-1.95 (m, 1H), 2.80 and 2.90 (2 singlets, 3H), 2.90-3.10 (m, 4H), 3.10-3.65 (m, 4H), 3.74 9S, 3H), 3.81 and 3,88 (2 doublets, J=10Hz, 1H), 5.93 (s, 2H), 6.72 (d, J=8Hz, 1H), 6.80-6.90 (m, 3H), 7.02 (2 doublets, J=2Hz, 1H), 7.80-7.90 (2 doublets, J=9Hz, 2H).

Example 49

Alternate Prepration of

Ethyl 2-(4-methoxybenzoyl)-4-nitromethyl-3-(1,3-benzodioxole-5-yl)butyrate

Example 49A

E-2-(3,4-Methylenedioxyphenyl)-1-nitroethene

To a stirred solution of piperonal (75g, 500 mmol) in methanol (120 mL) at 10 °C was added nitromethane (27.1 mL, 500 mmol, 1 eq) followed by the dropwise addition of sodium hydroxide (21 g, 525 mmol, 1.05 eq) in sufficient water to achieve a total volume of 50 mL while maintaining the temperature between 10-15 °C. The reaction mixture became cloudy, turning to a thick paste. The mixture was stirred for 30 minutes upon completion of the addition, and the mixture was then diluted with ice-water (~350 mL) maintaining the temperature below 5 °C, until solution was achieved. The resultant solution was poured in a narrow stream (such that it just failed to break into drops) into a rapidly stirred solution of 36% hydrochloric acid (100 mL) in water (150 mL). A yellow solid precipitated (nitrostyrene), and this was collected by filtration, washed with water (1.5 L) until the filtrate was neutral. The filter cake was air dried and then recrystallized from hot ethanol (3 L) to

yield E-2-(3,4-methylenedioxy)-nitrostyrene as yellow needles (53 g, 55%). ^1H NMR (300MHz, $CDCl_3$) δ 7.94 (1H, d, J=13.5Hz), 7.47 (1H, d, J=13.5Hz), 7.09 (1H, dd, J=7.5&2Hz), 7.01 (1H, d, J=2Hz), 6.87 (1H, d, J=7.5Hz), 6.06 (2H, s). MS (DCI/NH_3) m/e 194 $(M+H)^+$, 211 $(M+H+NH_3)^+$.

Example 49B

Ethyl 2-(4-methoxyphenyl)oxo-4-nitro-3-(3,4-methylenedioxyphenyl)butyrate

To a stirred solution of the nitrostyrene resulting from Example 49A (14.17 g, 73.34 mmol, 1.2 eq) in a mixture of propan-2-ol (75 mL) and tetrahydrofuran (175 mL) at room temperature was added successively a solution of ethyl (4-methoxybenzoyl)acetate (11.5 g, 51.7 mmol) in THF (50 mL) followed by 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (0.45 mL, 3.0 mmol, 0.05 eq). The resultant mixture was stirred at room temperature for 1 hour, then additional DBU (0.45 mL, 3.0 mmol, 0.05 eq) was added. The mixture was stirred a further 1 hour, then the volatiles were removed *in vacuo* and the residue purified by flash chromatography on 500 g silica gel, eluting with 20% ethyl acetate-hexanes changing to 25% ethyl acetate-hexanes as the product eluted. The solvents were removed *in vacuo* to yield the nitroketoester (19.36 g, 76%) as a viscous oil. Diastereomers were seen in the NMR. ^1H NMR (300 MHz, $CDCl_3$,) δ 8.06 (2H, d, J=9Hz), 7.89 (2H, d, J=9Hz), 6.96 (2H, d, J=9Hz), 6.91 (2H, d, J=9Hz), 6.77 (1H, dd, J=9Hz,3Hz), 6.73 (1H, d, J=9Hz), 6.65 (1H, d, J=3Hz), 5.95 (2H, s), 5.89 (1H, d, J=4Hz), 5.88 (1H, d, J=4Hz), 4.90-4.60 (3H, m), 4.39 (1H, m), 4.18 (2H, q, J=7Hz), 3.94 (2H, m), 3.80 (3H, s), 3.78 (3H, s), 1.19 (3H, t, J=7Hz), 0.99 (3H, t, J=7Hz), MS (DCI/NH_3) m/e 416 $(M+H)^+$, 433 $(M+H+NH_3)^+$.

Example 50

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(t-butyloxycarbonylmethyl)-pyrrolidine-3-carboxylic acid

To a stirred solution of the compound resulting from Example 1C (100 mg, 0.27 mmol) in acetonitrile (2 mL) was added successively diisopropylethylamine (70 µL, 0.40 mmol, 1.5 eq) and t-butyl bromoacetate (48 µL, 0.29 mmol, 1.1 eq). The mixture was stirred 2 hours, then the solvent was removed *in vacuo* to yield the crude diester. To a stirred solution of the diester in ethanol (1 mL) at room temperature was added 50% w/w sodium hydroxide (300 mg, 3.75mmol) in water. The mixture was stirred 2 hours, then the volatiles were removed *in vacuo*. The residue was dissolved in water (5 mL), and the solution was washed with ether. The aqueous phase was acidified with acetic acid (300 µL), and then extracted with ethyl acetate (2x). The combined organic extracts were dried (Na_2SO_4),

filtered, and concentrated to yield the title compound (74 mg, 60%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (2H, d, J=8Hz), 7.13 (1H, d, J=3Hz), 6.90 (1H, dt, J=3Hz, 8Hz), 6.88 (2H, d, J=8Hz), 6.76 (1H, d, J=8Hz), 5.96 (2H, s), 3.96 (1H, d, J=9Hz), 3.81 (3H, s), 3.58 (1H, ddd, J=12, 10Hz,3Hz), 3.52 (1H, dd, J=9Hz,3Hz), 3.32 (1H, d, J=17Hz), 3.08 (1H, t, J=10Hz), 2.92 (1H, dd, J=9Hz,7Hz), 2.83 (1H, d, J=17Hz). MS (DCI/NH_3) m/e 456 $(M+H)^+$.

Anal calc for $C_{29}H_{29}NO_7 \cdot 0.3\ H_2O$: C, 65.07; H, 6.48; N, 3.04. Found: C, 65.02; H, 6.42; N, 2.93.

Example 51

trans,trans-2-(4-Methoxyphenyl)-4-(1-naphthyl)-1-(N-methyl-N-propyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting naphthalene-1-carboxaldehyde for piperonyl in Example 49A. Rotational isomers are seen in the NMR. ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (1H, bd, J=8Hz), 7.86 (2H, d, J=8Hz),7.75 (1H, d, J=8Hz), 7.49 (3H, m), 7.34 (2H, dd, J=3Hz,9Hz), 6.83 (2H, dd, J=9Hz,2Hz), 4.50 (1H, m), 3.94 (1H, dd, J=9Hz,2Hz), 3.78 (3H, s), 3.65 (1H, m), 3.49 (1H, d, J=14Hz), 3.40-2.93 (5H, m), 2.91, 2.83 (3H, s), 1.48 (2H, sept, J=7Hz), 0.83, 0.77 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 461 $(M+H)^+$. Anal calcd for $C_{29}H_{29}NO_7 \cdot 0.5$ HOAc: C, 71.00; H, 6.99; N, 5.71. Found: C, 70.95; H, 7.00; N, 5.46.

Example 52

trans,trans-2-(4-Methoxyphenyl)-4-(2,3-dihydrobenzofuran-5-yl)-1-(N-methyl-N-propyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 52A

2,3-Dihydrobenzofuran-5-carboxaldehyde

To a stirred solution of α,α-dichloromethyl methyl ether (2.15 g, 19 mmol, 1.35 eq) in methylene chloride (30 mL) at -40 °C was added successively stannic chloride (1.65 g, 17 mmol, 1.2 eq) and 15 minutes later, a solution of 2,3-dihydrobenzofuran (1.68 g, 14 mmol) in CH_2Cl_2 (5 mL) maintaining the temperature at or below -35 °C. The mixture was warmed to 0 °C, stirred 1 hour, then poured into ice-water, and stirred a further 30 minutes. The mixture was diluted with ether, and the phases separated. The organic phase was concentrated *in vacuo*, and the residue purified by vacuum distillation to yield the title compound (1.25 g, 60%) as a colorless liquid. b.p. 119-121 °C at 0.3 mm Hg.

Example 52B

trans,trans-2-(4-Methoxyphenyl)-4-(2,3-dihydrobenzofuran-5-yl)-1-(N-methyl-N-propyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting the compound resulting from Example 52A for piperonal in Example 49A. Rotational isomers are seen in the NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (1H, d, J=8Hz), 7.28 (1H, m), 7.19 (1H, m), 6.87 (1H, d, J=8Hz), 6.73 (1H, d, J=8Hz), 4.56 (1H, t, J=8Hz), 3.83 (1H, d, J=10Hz), 3.80 (3H, s), 3.63 (1H, m), 3.4-3.0 (9H, m), 2.87, 2.84 (3H, s), 1.51 (2H, septet, J=7Hz), 0.88, 0.78 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 453 $(M+H)^+$. Anal calc for $C_{26}H_{32}N_2O_5 \cdot 0.25\ H_2O$: C, 68.33; H, 7.17; N, 6.13. Found: C, 68.60; H, 6.88; N, 5.80.

Example 53

trans,trans-2,4-Bis(4-methoxyphenyl)-1-(N-methyl-N-propyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 4-methoxybenzaldehyde for piperonal in Example 49A. Rotational isomers are seen in the NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (2H, d, J=7.5 Hz), 7.32 (2H, d, J=7.5 Hz), 6.86 (4H, m), 3.83 (1H, m), 3.81 (3H, s), 3.79 (3H, s), 3.64 (1H, m), 3.48-2.97 (6H, m), 2.87, 2.83 (3H, s), 2.85 (1H, m), 1.45 (2H, m), 0.84, 0.74 (3H, t, J=7.5 Hz). MS (DCI/NH_3) m/e 441 $(M+H)^+$. Anal calc for $C_{25}H_{32}N_2O_5 \cdot 0.5\ H_2O$: C, 66.80; H, 7.40; N, 6.23. Found: C, 67.15; H, 7.31; N, 6.00.

Example 54

trans,trans-2-(4-Methoxyphenyl)-4-(3,4-dimethoxyphenyl)-1-(N-methyl-N-propyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 3,4-dimethoxybenzaldehyde for piperonal in Example 49A. Rotational isomers are seen in the NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (2H, d, J=7.5 Hz), 7.07 (1H, d, J=2.0 Hz), 6.98 (1H, m), 6.85 (1H, d, 7.5 Hz), 6.82 (2H, d, 7.5 Hz), 3.91 (3H, s), 3.86 (3H, s), 3.83 (1H, m), 3.79 (3H, s), 3.64 (1H, m), 3.50-2.95 (6H, m), 2.87 (1H, m), 2.85, 2.83 (3H, s), 1.45 (2H, m), 0.84, 0.74 (3H, t, J=7.5 Hz). MS (DCI/NH_3) m/e 471 $(M+H)^+$. Anal calc for $C_{26}H_{34}N_2O_6 \cdot 0.5\ H_2O$: C, 65.12; H, 7.36; N, 5.84. Found: C, 65.22; H, 7.27; N, 5.59.

Example 55

trans,trans-2-(4-Methoxyphenyl)-4-(3-methoxyphenyl)-1-(N-methyl-N-propyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 3-methoxybenzaldehyde for piperonal in Example 49A. Rotational isomers are seen in the NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (2H, d, J=7.5 Hz), 7.24 (1H, t, J=7.5 Hz), 7.05 (2H, m), 6.85 (2H, dd, J=7.5&2 Hz), 6.76 (1H, m), 3.83 (1H, m), 3.81 (3H, s), 3.79 (3H, s), 3.64 (1H, m), 3.48-2.97 (6H, m), 2.87, 2.83 (3H, s), 2.85 (1H, m), 1.45 (2H, m), 0.84, 0.74 (3H, t, J=7.5 Hz). MS (DCI/NH_3) m/e 441 $(M+H)^+$. Anal calc for $C_{25}H_{32}N_2O_5 \cdot 0.5\ H_2O$: C, 66.80; H, 7.40; N, 6.23. Found: C, 66.76; H, 7.36; N, 6.05.

Example 56

trans,trans-2-(4-Methoxyphenyl)-4-(2-naphthyl)-1-(N-methyl-N-propyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting naphthylene-2-carboxaldehyde for piperonal in Example 49A. Rotational isomers are seen in the NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (4H, m), 7.69 (1H, m), 7.47 (2H, m), 7.37 (2H, dd, J=7.5&2 Hz), 6.85 (2H, dd, J=7.5&2 Hz), 3.90 (1H, d, J=8 Hz), 3.78 (3H, s), 3.57 (1H, m), 3.52-2.97 (6H, m), 2.93, 2.85 (3H, s), 2.90 (1H, m), 1.52 (2H, m), 0.86, 0.76 (3H, t, J=7.5 Hz). MS (DCI/NH_3) m/e 461 $(M+H)^+$. Anal calc for $C_{28}H_{32}N_2O_4 \cdot 0.5\ H_2O$: C, 71.62; H, 7.08; N, 5.97. Found: C, 71.58; H, 7.11; N, 6.01.

Example 57

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(ethylsulfinyl)ethyl)-pyrrolidine-3-carboxylic acid

To the compound resulting from Example 1C (100 mg, 0.27 mmol) and 2-chloroethyl ethyl sulfide (67.5 mg, 0.5 mmol, 2 equivalents) dissolved in 6 mL of acetonitrile was added 10 mg of KI and 0.5 mL of diisopropylethylamine. The mixture was refluxed for 4 hours and then concentrated *in vacuo*. The residue obtained was purified by flash chromatography on silica gel eluting with 4:1 hexane-ethyl acetate to afford 93 mg (75%) of the ethylthioethyl compound.

To the sulfide (90 mg, 0.2 mmol) dissolved in 5 mL of CH_2Cl_2 in an ice bath was added 68 mg of 3-chloroperoxybenzoic acid. The mixture was stirred for 40 minutes in the ice bath and for 3 hours at room temperature. A 10% solution of sodium hydroxide (2 mL) was added, and the mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water and brine, dried over sodium sulfate and concentrated in vacuo. The residue obtained was chromatographed on silica gel eluting with EtOAc and 10% MeOH in CH_2Cl_2 to afford the sulfoxide (62 mg, 65%).

The ethyl ester was hydrolyzed by the procedure described in Example 1D to afford the title compound as a diastereomeric mixture. m.p. 61-63 °C. MS (DCI/NH_3) m/e 446 $(M+H)^+$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25, 1.32 (t, J=9Hz, 3H), 2.45-2.75 (m, 4H), 2.84-2.96 (m, 3H), 3.02-3.08 (m, 1H), 3.32, 3.36 (d, J=3Hz, 1H), 3.47-3.58 (m, 2H), 3.65, 3.68 (d, J=7.5Hz, 1H), 3.76, 3.80 (s, 3H), 5.94 (s, 2H), 6.72 (d, J=7.5Hz, 1H), 3.84-3.89 (m, 3H), 7.02 (d, J=6Hz, 1H), 7.30, 7.34 (d, J=7.5Hz, 2H).

Example 58

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(isopropylsulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

To 2-bromoethylamine hydrobromide (1 mmol) suspended in anhydrous CH_3CN was added 1 equivalent of Et_3N. The mixture was stirred for 30 minutes and then 1 equivalent of isopropyl sulfonyl chloride and 1 equivalent of Et_3N were added. The resulting mixture was stirred for 2 hours at room temperature and then added to a solution of the compound resulting from Example 1C (185 mg, 0.5 mmol) in 3 mL of CH_3CN. The mixture was warmed at 50-60 °C for 2 hours, cooled to room temperature, treated with water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried and concentrated *in vacuo*. The residue obtained was chromatographed on silica gel eluting with 3:2 hexane-EtOAc to give 195 mg (75%) of the ethyl ester. The ethyl ester (160 mg, 0.31 mmol) was hydrolyzed by the procedure described in Example 1D to afford the title compound (133 mg, 88%). m.p. 94-96 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.26 (d, J=6Hz, 6H), 1.97 (s, 1H), 2.38 (m, 1H), 2.77 (m, 1H), 2.88 (t, J=9Hz, 1H), 3.04 (m, 1H), 3.14 (t, J=7.5Hz, 2H), 3.35 (m, 2H), 3.46 (m, 1H), 3.58 (m, 1H), 3.78 (s, 3H), 5.92 (s, 2H), 6.74 (d, J=9Hz, 1H), 6.86 (dd, J=9Hz,3Hz, 1H), 6.92 (d, J=9Hz, 2H), 7.00 (d, J=3Hz, 1H), 7.36 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e $(M+H)^+$.

Example 59

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(isobutoxy)ethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 1D from the compound resulting from Example 1C and 2-(isobutoxy)ethyl bromide. m.p. 68-70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, J=6Hz, 6H), 1.82 (quintet, J=6Hz, 1H), 2.22 (m, 2H), 2.72-2.79 (m, 1H), 2.86-2.95 (m, 2H), 3.13 (d, J=6Hz, 2H), 3.45-3.56 (m, 4H), 3.68 (d, J=9Hz, 1H), 3.79 (s, 3H), 5.94 (s, 2H), 6.72 (d, J=7.5Hz, 1H), 6.85 (dd, J=9Hz, 7.5 Hz, 3H), 7.08 (s, 1H), 7.34 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 442 $(M+H)^+$.

Example 60

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(butylsulfonyl)-pyrrolidine-3-carboxylic acid

To 100 mg (0.271 mmol) of the compound resulting from Example 1C dissolved in 10 mL of THF was added 1-butanesulfonyl chloride (46.7 mg, 1.1 equivalents) and diisopropylethylamine (53 mg, 1.5 equivalents). The resulting mixture was stirred for 2.5 hours at room temperature and then the solvent evaporated. The crude product was purified by flash chromatography on silica gel eluting with 3:2 hexane-EtOAc to afford 120 mg (90%) of the ethyl ester.

The ester (120 mg, 0.244 mmol) was dissolved in 1 mL of EtOH, and a solution of 100 mg of NaOH in 1 mL of water was added. The mixture was stirred for 3 hours at room temperature and then concentrated under reduced pressure. Water (5 mL) was added and the solution was washed with ether to remove any unhydrolyzed *trans-cis* isomer. The aqueous solution was acidified to pH~6 with acetic acid and then extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure to afford the pure title compound (60 mg, 53%) as a white solid. m.p. 67-69 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J=7.5Hz, 3H), 1.20-1.33 (m, 2H), 1.58-1.68 (m, 2H), 2.48-2.69 (m, 2H), 3.28 (dd, J=9Hz, 1H), 3.49 (t, J=12Hz, 1H), 3.65 (dd, J=12Hz, 1H), 3.82 (s, 3H), 4.32 (dd, J=12Hz, 1H), 5.17 (d, J=9Hz, 2H), 5.95 (s, 2H), 6.70-6.78 (m, 3H), 6.92 (d, J=9Hz, 2H), 7.35 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 462 $(M+H)^+$.

Example 61

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-methyl-N-isopropylcarbonylamino)ethyl)-pyrrolidine-3-carboxylic acid

Example 61A

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-bromoethyl)-pyrrolidine-3-carboxylic acid ethyl ester

To the mixture of cis,trans and *trans,trans* pyrrolidines resulting from Example 1C (400 mg) dissolved in 9 mL of 1,2-dibromoethane was added 0.7 mL of diisopropylethylamine and 30 mg of sodium iodide. The resultant mixture was heated at 100 °C for 1 hour, and then the solvents were removed *in vacuo*. The residue was taken up in EtOAc and washed sequentially with water and brine, dried and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 4:1 hexane-EtOAc to give 470 mg of the title product.

Example 61B

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(methylamino)ethyl)-pyrrolidine-3-carboxylic acid ethyl ester

To the compound resulting from Example 61A (450 mg) dissolved in 10 mL of EtOH was added 0.5 mL of 40% aqueous methylamine and 50 mg of sodium iodide. The mixture was heated at 80 °C for 1 hour, and then the solvents were removed *in vacuo*. The residue was taken up in EtOAc and washed sequentially with water and brine, dried and concentrated *in vacuo*. The resultant product was carried on without further purification.

Example 61C

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-methyl-N-isobutyrylamino)ethyl)-pyrrolidine-3-carboxylic acid

To the compound resulting from Example 61B (~150 mg) dissolved in 5 mL of 1,2-dichloroethane was added 0.3 mL of diisopropylethylamine. The solution was cooled to -40 °C, isobutyryl chloride (0.17 mL) was added, the bath was removed, and the solution was allowed to warm to ambient temperature and stirred for 15 hours. The solvent was removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with 1:1 sodium bicarbonate solution/water and brine, dried and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with a gradient 1:1 EtOAc-hexanes going to EtOAc and finally using 10% MeOH-EtOAc.

The ester was dissolved in 1.5 mL of EtOH; 0.75 mL of a 17% aqueous NaOH solution was added, and the resultant mixture was stirred at ambient temperature for 3 hours. The solvents were removed *in vacuo*; the residue was taken up in water and washed with ether. The aqueous phase was acidified with 1 N H_3PO_4 to pH 3 and extracted twice with ether. The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* to provide 82 mg of the title compound as a white foam. Rotamers were seen in the NMR. ^{1}H NMR ($CDCl_3$, 300 MHz) of the major rotamer δ 1.06 (d, 3H, J=10Hz), 1.12 (d, 3H, J=10Hz), 2.15 (m, 1H), 2.5-3.0 (m, 3H), 2.91 (s, 3H), 3.32 (m, 2H), 3.50 (m, 2H), 3.65 (m, 2H), 3.77 (s, 3H), 5.92 (s, 2H), 6.73 (d, 1H, J=8Hz), 6.75-6.9 (m, 4H), 6.96 (d, 1H, J=2Hz), 7.29 (m, 1H). MS (DCI/NH_3) m/z 469 $(M+H)^+$. Analysis calcd for $C_{26}H_{32}N_2O_6 \cdot 0.3$ TFA: C, 63.55; H, 6.48; N, 5.57. Found: C, 63.44; H, 6.71; N, 5.24.

Example 62

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-methyl-N-propionylamino)ethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 61 substituting propionyl chloride for isobutyryl chloride in Example 61C. ^{1}H NMR ($CDCl_3$,

300 MHz) of the major rotamer δ 1.13 (t, 3H, J=8Hz), 2.19 (m, 1H), 2.30 (m, 2H), 2.65-3.0 (m, 3H), 2.85 (s, 3H), 3.25-3.4 (m, 2H), 3.5-3.7 (m, 3H), 3.79 (s, 3H), 5.92 (s, 2H), 6.74 (d, 1H, J=8Hz), 6.75-6.9 (m, 4H), 7.00 (bd s, 1H), 7.29 (bd s, 1H). MS (DCI/NH_3) m/z 455 $(M+H)^+$. Analysis calcd for $C_{25}H_{30}N_2O_6 \cdot 1.0\ H_2O$: C, 63.55; H, 6.83; N, 5.93 . Found: C, 63.55; H, 6.52; N, 5.73.

Example 63

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-benzylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared. ^1H NMR ($CDCl_3$, 300 MHz) of the major rotamer δ 2.79 (s, 3H), 2.8-3.2 (m, 2H), 3.48 (m, 2H), 3.61 (m, 2H), 3.77 (s, 3H), 3.78 (m, 1H), 4.3-4.5 (m, 2H), 5.95 (d, 2H, J=2Hz), 6.7-6.9 (m, 4H), 7.00 (m, 1H), 7.15-7.35 (m, 7H). MS (FAB/NBA) m/z 503 $(M+H)^+$. Anal calcd for $C_{29}H_{30}N_2O_6 \cdot 0.5\ H_2O$: C, 68.36; H,5.74; N, 5.50. Found: C,68.41; H, 5.74; N, 5.36 .

Example 64

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-butylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared. ^1H NMR ($CDCl_3$, 300 MHz) of the major rotamer δ 0.88 (t, 3H, J=7Hz), 1.06 (t, 3H, J=7Hz), 1.27 (m, 2H), 1.45 (m, 2H), 2.8-3.6 (m, 11H), 3.79 (s,3H), 3.80 (m, 1H), 5.92 (bd s, 2H), 6.75 (d, 1H, J=8Hz), 6.85 (d, 1H, J=8Hz), 6.92 (d, 2H, J=8Hz), 7.03 (s, 1H), 7.33 (d, 1H, J=8Hz). MS (DCI/NH_3) m/z 483 $(M+H)^+$. Anal calcd for $C_{27}H_{34}N_2O_6 \cdot 0.5$ HOAc: C, 65.61; H,7.08; N, 5.46. Found: C,65.51; H, 6.70; N, 5.66.

Example 65

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-(2,2-dimethylpropyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1 the title compound was prepared. ^1H NMR ($CDCl_3$, 300 MHz) of the major rotamer δ 0.90 (s, 9H), 2.8-3.1 (m, 4H), 2.94 (s, 3H), 3.3-3.5 (m, 3H), 3.61 (m, 1H), 3.80 (s, 3H), 3.82 (m, 1H), 5.94 (bd s, 2H), 6.74 (d, 1H, J=8Hz), 6.86 (d, 2H, J=8Hz), 6.87 (m, 1H), 7.03 (d, 1H, J=2Hz), 7.33 (d, 2H, J=8Hz). MS (DCI/NH_3) m/z 483 $(M+H)^+$.

Example 66

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-methyl-N-butylsulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

To the compound resulting from Example 61B (60 mg, 0.13 mmol) dissolved in 5 mL of CH_3CN was added 0.2 mL of Et_3N and 22 mg (0.143 mmol, 1.1 equivalents) of 1-butanesulfonyl chloride. The mixture was stirred for 1 hour at room temperature and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 1:1 EtOAc-hexane to yield 64 mg (90%) of the ester. Ester hydrolysis by the procedure described in Example 1D afforded the title compound. m.p. 64-66 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J=7.5Hz, 3H), 1.39 (hexad, J=7.5Hz, 2H), 1.68-1.76 (m, 2H), 2.16-2.25 (m, 1H), 2.72 (s, 3H), 2.75-2.92 (m, 5H), 3.12-3.20 (m, 1H), 3.25-3.34 (m, 1H), 3.46-3.55 (m, 2H), 3.65 (d, J=9Hz, 1H), 3.78 (s, 3H), 5.53 (s, 2H), 6.72 (d, J=7.5Hz, 1H), 6.82 (dd, J=7.5Hz,3Hz, 1H), 6.86 (d, J=9Hz, 2H), 7.02 (d, J=3Hz, 1H), 7.34 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 519 $(M+H)^+$.

Example 67

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-methyl-N-propylsulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 66 substituting 1-propanesulfonyl chloride for 1-butanesulfonyl chloride. m.p. 69-70 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, J=7.5Hz, 3H), 1.78 (hexad, J=7.5Hz, 2H), 2.18-2.26 (m, 1H), 2.72 (s, 3H), 2.75-2.95 (m, 6H), 3.13-3.22 (m, 1H), 3.25-3.35 (m, 1H), 3.47-3.58 (m, 2H), 3.66 (d, J=9Hz, 1H), 3.80 (s, 3H), 5.96 (s, 2H), 6.74 (d, J=7.5Hz, 1H), 6.84 (d,d, J=7.5Hz, 3Hz, 1H), 6.87 (d, J=9Hz, 2H), 7.04 (d, J=3Hz, 1H), 7.43 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 505 $(M+H)^+$.

Example 68

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(propylsulfonyl)ethyl)-pyrrolidine-3-carboxylic acid

To 1-propanethiol (3.5 g, 46.05 mmol) dissolved in 10 mL of anhydrous THF was added 632 mg (26.32 mmol) of NaH in portions under a nitrogen atmosphere. The mixture was heated at 60-70 °C for 1 hours. To this mixture was added the compound resulting from Example 61A (180 mg, 0.38 mmol) in 2 mL THF. Heating was continued at 60-70 °C for an additional 2 hours, and then the volatiles were removed under reduced pressure. The crude propylthioethyl adduct was purified by flash chromatography on silica gel eluting with 3:2 hexane-EtOAc to give 170 mg (95%).

To a solution of 170 mg (0.36 mmol) of the sulfide and 93 mg (0.8 mmol) of N-methylmorpholine N-oxide (NMO) in a mixture of 20 mL of acetone and 5 mL of H_2O was added a solution of osmium tetroxide (10 mg) in 0.3 mL of t-butanol. The resulting mixture

was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography afforded 177 mg (98%) of the ethyl ester which was hydrolyzed by the procedures described in Example 1D to afford the title compound. m.p. 73-75 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (t, J=7.5Hz, 3H), 1.78 (hexad, J=7.5Hz, 2H), 2.59-2.66 (m, 1H), 2.84-3.08 (m, 7H), 3.43 (dd, J=9Hz, 3Hz, 1H), 3.53-3.60 (m, 1H), 3.68 (d, J=9Hz, 1H), 3.82 (s, 3H), 5.96 (s, 2H), 6.75 (d, J=7.5Hz, 1H), 6.82 (dd, J=7.5Hz, 3Hz, 1H), 6.88 (d, J=9Hz, 2H), 6.99 (d, J=3Hz, 1H), 7.32 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 476 $(M+H)^+$.

Example 69

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-N-(*trans*-5-methylhex-2-enyl)-pyrrolidine-3-carboxylic acid

Example 69A

trans-5-Methylhex-2-enoic acid ethyl ester

Oil dispersion sodium hydride (0.85 g) was washed with hexanes and suspended in THF (20 mL), and the mixture was cooled in an ice bath to 0 °C. Diisopropyl(ethoxycarbonylmethyl) phosphonate (5.0 mL) was added slowly and the mixture stirred for 20 minutes at 0 °C. Isovaleraldehyde (2.0 mL) in THF (5 mL) was added dropwise over five minutes. The ice bath was removed and the mixture stirred for 18 hours at ambient temperature. Saturated ammonium chloride solution (50 mL) was added and the mixture extracted with diethyl ether (3 x 50 mL). The ether extracts were combined, dried with Na_2SO_4, and evaporated to give a colorless oil which was purified by flash chromatography on silica gel eluting with hexanes. The title compound was isolated as a colorless oil (2.1 g).

Example 69B

trans-5-Methylhex-2-en-1-ol

The compound resulting from Example 69A (2.0 g) was dissolved in toluene and cooled to 0 °C in an ice bath. Diisobutylaluminum hydride (1.5 N in toluene, 20 mL) was added dropwise and the solution stirred at 0 °C for two hours. Citric acid solution (25 mL) was added very slowly to the cooled solution. The resulting mixture was stirred for 18 hours at ambient temperature. Diethyl ether (50 mL) was added, the solids removed by filtration and washed with additional ether (2 x 25 mL). The filtrate was extracted with ether (2 x 25 mL). The ether extractions and washings were combined, dried, and evaported to give a

colorless oil which was purified by flash chromatography on silica gel eluting with 25% EtOAc-hexanes. The title compound was isolated as a colorless oil (1.25 g).

Example 69C

trans-1-Bromo-5-methylhex-2-ene

The compound resulting from Example 69B (1.0 g) was dissolved in diethyl ether and cooled to 0 °C in an ice bath. Phosphorus tribromide (2.5 g, 0.87 mL) was added dropwise and the solution stirred at 0 °C for two hours. The solution was poured onto ice, the layers separated, and the aqueous layer extracted with additional ether (3 x 25 mL). The ether layers were combined, dried, and evaporated to give a colorless oil which was used without further purification (0.95 g).

Example 69D

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-N-(*trans*-5-methylhex-2-enyl)-pyrrolidine-3-carboxylic acid

The title compound was synthesized using the methods detailed in Example 1D but substituting the compound resulting from Example 69C for N-propyl bromoacetamide. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, 6H, J=8Hz), 1.57 (heptet, 1H, J=8Hz), 1.87 (t, 2H, J=6Hz), 2.60 (dd, 1H, J=8Hz,14Hz), 2.86 (t, 1H, J=10Hz), 2.96 (dd, 1H, J=8Hz,10Hz), 3.20 (dd, 1H, J= 5Hz,14Hz), 3.29 (dd, 1H, J=3Hz,10Hz), 3.50 (m, 1H), 3.70 (d, 1H, J=10Hz), 3.78 (s, 3H), 5.47 (m, 2H), 5.93 (s, 2H), 6.71 (d, 1H, J=8Hz), 6.83 (d, 3H, J=9Hz), 7.05 (s, 1H), 7.32 (d, 2H, J=9Hz). MS (DCI/NH_3) m/e 438 $(M+H)^+$. Anal calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.16; H, 7.24; N, 3.17.

Example 70

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-N-(*trans*-3,5-dimethylhex-2-enyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 69 but substituting 4-methyl-2-pentanone for isovaleraldehyde in Example 69A, which gave ~7:1 mixture of trans/cis olefins. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product (and its diastereomer) as a white solid. ^{1}H NMR of the major (trans) isomer: ($CDCl_3$, 300 MHz) δ 0.83 (d, 6H, J=8Hz), 1.56 (s,3H), 1.74 (m, 1H), 1.92 (d, 2H, J=6Hz), 3.3-3.5 (m, 3H), 3.6-3.8 (m,4H), 3.78 (s, 3H), 3.9-4.0 (m, 1H), 5.22 (m, 1H), 5.90 (d, 2H, J=12Hz), 6.63 (m, 1H), 6.78 (m, 3H), 6.95 (s, 1H), 7.45 (d, 3H, J=8Hz). MS (DCI/NH_3) m/e 438 $(M+H)^+$. Anal calcd for $C_{27}H_{33}NO_5 \cdot 1.0$ TFA: C, 61.59; H, 6.06; N, 2.48. Found: C, 61.36; H, 6.10; N, 2.34.

Example 71

<u>*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(4-heptylcarbonylmethyl)-pyrrolidine-3-carboxylic acid</u>

Example 71A

<u>1-Chloro-3-propyl-2-hexanone</u>

To 2-propylpentanoic acid (156.6 μl, 1.00 mmol) dissolved in anhydrous dichloromethane (2 mL) was added DMF (3 μL, 4 mole %), and the solution was cooled to 0 °C under a nitrogen atmosphere. To the solution was added oxalyl chloride (94.3 μL, 1.08 mmol) dropwise over a few minutes. The reaction was stirred 18 hours while warming to ambient temperature. The mixture was cooled to 0 °C and excess ~0.3 <u>M</u> ethereal diazomethane solution was added. The reaction mixture was stirred 18 hours while warming to ambient temperature. The reaction mixture was washed with 1 <u>M</u> aqueous sodium carbonate solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in ether (2 mL) and cooled to 0 °C under a nitrogen atmosphere. Hydrogen chloride as a 4 <u>N</u> solution in dioxane (275 μL, 1.10 mmol) was added dropwise over a few minutes. The reaction was stirred 18 hours while warming to ambient temperature. The reaction mixture was concentrated under reduced pressure and the residual oil was used in the next step without further purification.

Example 71B

<u>*trans,trans*-Ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(4-heptylcarbonylmethyl)-pyrrolidine-3-carboxylate</u>

To the compound resulting from Example 71A (1.00 mmol, maximum theoretical yield) was added a solution of the *trans,trans* ethyl carboxylate from Example 1C (295 mg, 0.80 mmol as a 50 % solution in toluene), diisopropylethylamine (700 μL, 4.00 mmol) and acetonitrile (4 mL). To the resulting solution was added sodium iodide (12 mg, 10 mole %), and the reaction mixture was stirred 18 hours under a nitrogen atmosphere at ambient temperature. Additional sodium iodide (24 mg, 20 mole %) and acetonitrile (4 mL) were added, and the reaction mixture was heated at 45-50 °C with stirring for 18 hours. The reaction mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel eluting with 1:9 ethyl acetate-hexane to give 237 mg (46%) of the title compound as a yellow oil.

Example 71C

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(4-heptylcarbonylmethyl)-pyrrolidine-3-carboxylic acid

To the compound resulting from Example 71B (231 mg, 0.4532 mmol) dissolved in ethanol (10 mL) was added a solution of lithium hydroxide (38 mg, 0.9065 mmol) in water (2.5 mL). The solution was stirred for 18 hours under a nitrogen atmosphere, additional lithium hydroxide (19 mg, 0.4532 mmol) in water (0.5 mL) was added, and stirring was continued 24 hours. The reaction mixture was concentrated under reduced pressure to remove the ethanol, and the aqueous residue was diluted with water (45 mL) and washed with ether (50 mL). The aqueous layer was neutralized with 1 N hydrochloric acid to cloudiness and then 10% aqueous citric acid was added to adjust the pH to ~5. This solution was then extracted with 10% ethanol in chloroform (4 x 25 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel eluted with 1:1 ethyl acetate-hexane to give 86 mg (39%) of the title compound as an off white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73-0.97 (m, 6H), 1.03-1.33 (m, 6H), 1.36-1.58 (m, 2H), 2.46 (m, 1H), 2.80-2.98 (m, 3H), 3.38-3.64 (m, 3H), 3.75-3.90 (m, 1H), 3.79 (s, 3H), 5.94 (s, 2H), 6.75 (d, 1H), 6.86 (d, 2H), 6.92 (d, 1H), 7.12 (s, 1H), 7.32 (d, 2H). MS (FAB) m/e 482 $(M+H)^+$. Anal calcd for $C_{28}H_{35}NO_6$: C, 69.83; H, 7.32; N, 2.91. Found: C, 69.57; H, 7.41; N, 2.73.

Example 72

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(valerylmethyl)-pyrrolidine-3-carboxylic acid

Example 72A

1-Chloro-2-hexanone

Using the procedure described in Example 71A and substituting pentanoic acid for 2-propylpentanoic acid afforded the title compound as an oil which was used in the next step without further purification.

Example 72B

trans,trans-Ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxole-5-yl)-1-(valerylmethyl)-pyrrolidine-3-carboxylate

Substituting the compound resulting from Example 72A for 1-chloro-3-propyl-2-hexanone and using the procedure described in Example 71B, except deleting the first addition of sodium iodide, stirring 18 hours at ambient temperature and purifying by silica gel chromatography eluting with 3:17 ethyl acetate-hexane, the title compound 305 mg (65%) was obtained as a yellow oil.

Example 72C

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(valerylmethyl)-pyrrolidine-3-carboxylic acid

By substituting the compound resulting from Example 72B for *trans,trans*-Ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(4-heptylcarbonylmethyl)-pyrrolidine-3-carboxylate and using the procedure described in Example 71C, except only one solution of lithium hydroxide (81.5 mg, 1.942 mmol) in water (3.5 mL) was added followed by stirring for 18 hours, the title compound 130 mg (46%) was obtained as an off white powder. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H), 1.26 (m, 2H), 1.49 (m, 2H), 2.37 (m, 2H), 2.79-2.98 (m, 3H), 3.31-3.49 (m, 2H), 3.56 (m, 1H), 3.77, 3.79 (d,s, 4H), 5.94 (s, 2H), 6.75 (d, 1H), 6.81-6.93 (m, 3H), 7.09 (d, 1H), 7.33 (d, 2H). MS (FAB) m/e 440 $(M+H)^+$. Anal. calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 67.95; H, 6.64; N, 3.05.

Example 73

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(3,4-dimethoxybenzyl)-N-methylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 73A

trans,trans- and cis,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((3,4-dimethoxybenzyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid ethyl ester

Using the procedure of Example 1D, paragraph 1, substituting 3,4-dimethoxybenzyl bromoacetamide for dipropyl bromoacetamide, the desired product mixture was obtained as a white foam in 81% yield.

Example 73B

trans,trans- and cis,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(3,4-dimethoxybenzyl)-N-methylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid ethyl ester

The resultant product from Example 73A (220 mg, 0.404 mmol) was dissolved in 2 mL dry THF and added dropwise to a stirred, cooled (0 °C) suspension of sodium hydride (23 mg of a 60% by weight mineral oil suspension, 16.5 mg, 0.69 mmol) in 0.2 mL THF, under an argon atmosphere. The resulting mixture was stirred at 0 °C for 1 hour, then methyl iodide (28 μL, 64 mg, 0.45 mmol) was added. The reaction mixture was stirred at 0 °C for 45 minutes. TLC (Et_2O) indicated incomplete reaction. An additional portion of methyl iodide

(28 μL, 64 mg, 0.45 mmol) and dry 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (50 μL, 0.41 mmol) were added. The reaction mixture was stirred at ambient temperature for 2 days. The reaction was poured into 25 mL of 0.5 M aqueous citric acid and extracted with 2 x 25 mL EtOAc. The combined organic extrracts were washed sequentially with 30 mL water and 30 mL brine, then dried (Na_2SO_4), filtered and concentrated under reduced pressure to produce 270 mg of crude material. Flash chromatography on silica gel eluting with Et_2O gave the title compounds as an inseparable mixture in 43% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.79 (s) and 2.81 (s), for the N-CH_3 signals. MS m/z 591 $(M+H)^+$.

Example 73C

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(3,4-dimethoxybenzyl)-N-methylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid

To the resultant compound from Example 73B (98 mg, 0.17 mmol) dissolved in 1 mL EtOH and cooled to 0 °C was added a solution of lithium hydroxide monohydroxide (17 mg, 0.41 mmol) in 0.5 mL H_2O. The resulting solution was stirred under a nitrogen atmosphere for 16 hours. The solution was concentrated *in vacuo*, and the residue was partitioned between 15 mL H_2O and 15 mL Et_2O. The aqueous phase was extracted with 5 mL Et_2O, then the aqueous phase was acidified with 10% aqueous citric acid. The acidic aqueous phase was saturated with NaCl and extracted with 3 x 15 mL EtOAc. The EtOAc extracts were combined, dried (Na_2SO_4), then filtered and concentrated *in vacuo* to give 40 mg (42%) of the title compound as a white foam. ^1H NMR (CD_3OD, 300 MHz, two rotameric forms) δ 2.85 (s, 3H), 2.94-3.25 (br m, 3H), 3.35-3.70 (br m) and 3.64 (s, 4 H total), 3.70-3.97 (br m), 3.74 (s), 3.76 (s), 3.78 (s), 3.79 (s), 3.81 (s), and 4.03 (br d, J=14 Hz, 8H total), 4.43 (AB, 1H), 5.91 (s) and 5.93 (s, 2H total), 6.50-6.60 (m, 1H), 6.67-7.02 (br m, 6H), 7.29 (br d) and 7.35 (br d, 2H total). HRMS calcd for $C_{31}H_{35}N_2O_8$ $(M+H)^+$: 563.2393. Found: 563.2385.

Example 74

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(3,4-dimethoxybenzyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The procedure of Example 73C was used, with the substitution of the resultant compound from Example 73A for the resultant compound from Example 73B, to provide the title compound. ^1H NMR (CD_3OD, 300 MHz) δ 2.85 (d, J=16Hz, 1H), 2.92 (br t, J=9Hz, 1H), 2.98 (br t, J=10Hz, 1H), 3.32-3.39 (br m, 2H), 3.54-3.65 (br m, 1H), 3.67 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 3.85 (d, J=10 Hz, 1H), 4.21 (d, J=15Hz, 1H), 4.41 (d, J = 15Hz, 1H), 5.91 (s, 2H), 6.67 (d, J=8Hz, 1H), 6.75-6.95 (m, 7H), 7.33-7.40 (m, 2H). HRMS calcd for $C_{30}H_{32}N_2O_8$ $(M+H)^+$: 549.2237. Found: 549.2224.

Example 75

(2R,3R,4R)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((1R)-1-(N,N-dipropylaminocarbonyl)-1-butyl)pyrrolidine-3-carboxylic acid

Example 75A

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((1R)-1-(benzyloxycarbonyl)butyl)pyrrolidine-3-carboxylic acid ethyl ester

The procedure of Fung, et. al., J. Med. Chem., 35(10): 1722-34 (1992) was adapted. The resultant compound from Example 6A (103 mg, 0.279 mmol) was dissolved in 0.7 mL of nitromethane and 0.7 mL of H_2O, and ammonium carbonate (34 mg, 0.35 mmol) and (2S)-benzyl 2-bromopentanoate (78 mg, 0.30 mmol) were added. The reaction was refluxed for 24 hours. The reaction was partitioned between 15 mL of 1 M aqueous Na_2CO_3 and 25 mL of CH_2Cl_2. The aqueous phase was extracted with 2 x 10 mL CH_2Cl_2, and the combined organic phases were washed with 15 mL brine, dried (Na_2SO_4), then filtered and concentrated under reduced pressure to a brown oil (169 mg). The crude product was purified by silica gel chromatography eluting with 3:1 CH_2Cl_2-hexane to produce 106 mg (68%) of the title compound as a waxy solid. ^1H NMR indicated the presence of two diastereomeric products.

Example 75B

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((1R)-1-(N,N-dipropylaminocarbonyl)-1-butyl)pyrrolidine-3-carboxylic acid ethyl ester

The resultant compound from Example 75A (101 mg, 0.180 mmol) and 30 mg of 10% palladium on charcoal were stirred in 2 mL EtOAc under 1 atmosphere of H_2 for 4 hours. The reaction mixture was filtered through a plug of Celite, using 15 mL MeOH to wash the catalyst. The combined filtrate and wash were concentrated *in vacuo* to give 81.4 mg (96%) of the crude acid as a white solid.

The above crude acid was combined with HOBt hydrate (41 mg, 0.27 mmol), dipropylamine (26 mg, 0.26 mmol), and 4-methylmorpholine (37 mg, 0.37 mmol) in 2 mL dry DMF. The solution was cooled to -15 °C, then 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (44 mg, 0.23 mmol) was added. The mixture was stirred at -15 °C and allowed to warm slowly to room temperature overnight. The solvent was removed by distillation under reduced pressure, and the residue was partitioned between 20 mL EtOAc and 10 mL of 1 M aqueous Na_2CO_3. The organic phase was washed with 10 mL of brine, dried (Na_2SO_4), then filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 1:2 Et_2O-hexane. Further purification of overlap fractions by preparative TLC eluting with 1:2 Et_2O-

hexane yielded 32 mg (34%) of a less polar product, and 44 mg (46%) of a more polar product.

Example 75C

(2R,3R,4R)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((1R)-1-(N,N-dipropylaminocarbonyl)-1-butyl)pyrrolidine-3-carboxylic acid

The procedure of Example 73C was followed, with the substitution of the less polar isomer from Example 75B for the resultant product from Example 73B, to provide the title compound in 94% yield. $[\alpha]_D$ = -52° (c=0.235, CH_3OH). ^1H NMR (CD_3OD, 300 MHz) δ 0.55 (t, J=7Hz, 3H), 0.87 (t, J=7Hz) and 0.87-0.94 (m, 6H total), 1.03-1.25 (br m, 2H), 1.25-1.68 (br m, 4H), 1.90-2.07 (br m, 1H), 2.75-2.94 (br m, 2H), 2.94-3.02 (br m, 2H), 3.20-3.40 (m, overlapping with CD_2HOD signal), 3.40-3.60 (br m, 2H), 3.79 (s, 3H), 4.04 (br d, J=9 Hz, 1H), 5.92 (dd, J=3,5 Hz, 2H), 6.72 (d, J=8 Hz, 1H), 6.79 (dd, J=1.5,8 Hz, 1H), 6.92-6.98 (br m, 3H), 7.29-7.39 (m, 2H). MS m/z 525 $(M+H)^+$.

Example 76

(2S,3S,4S)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((1R)-1-(N,N-dipropylaminocarbonyl)-1-butyl)pyrrolidine-3-carboxylic acid

The procedure of Example 73C was followed, with the substitution of the more polar isomer from Example 75B for the resultant product from Example 73B, to provide the title compound in 88% yield. $[\alpha]_D$ = +58° (c=0.37, CH_3OH). ^1H NMR (CD_3OD, 300 MHz) δ 0.57 (br t, J=7Hz, 3H), 0.88-0.98 (m, 6H), 1.08-1.35 (br m, 2H), 1.35-1.68 (br m, 4H), 1.75-1.90 (br m, 1H), 2.75-2.86 (br m, 2H), 3.10-3.30 (br m, 2H), 3.51-3.65 (br m, 2 H), 3.69 (s, 3H), 4.03-4.16 (br m, 2H), 5.91 (s, 2H), 6.71-6.83 (m, 2H), 6.86-6.97 (m, 3H), 7.32 (br d, J=9Hz, 2H). MS m/z 525 $(M+H)^+$.

Example 77

(2S,3S,4S)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((1S)-1-(N,N-dipropylaminocarbonyl)-1-butyl)pyrrolidine-3-carboxylic acid

Example 77A

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((1S)-1-(N,N-dipropylaminocarbonyl)-1-butyl)pyrrolidine-3-carboxylic acid ethyl ester

(2R)-N,N-dipropyl 2-hydroxypentanamide (106 mg, 0.528 mmol, made by standard procedure) was dissolved in 2 mL THF under an argon atmosphere, diisopropylethylamine (75 mg, 0.58 mmol) was added, then the solution was cooled to -20 °C. Trifluoromethanesulfonic anhydride (95 μL, 159 mg, 0.565 mmol) was added to the cooled

solution over 1 minute, and the reaction mixture was stirred at -20 °C for 1 hour, and at room temperature for an additional 1 hour. The resulting slurry was recooled to 0 °C, and a solution of the resultant compound from Example 6A (195 mg, 0.528 mmol) and diisopropylethylamine (101 μL, 75 mg, 0.58 mmol) in 3 mL of CH_2Cl_2 was added. The reaction was stirred at 0 °C for 3 hours and for an additional 2 days at room temperature. TLC (Et_2O-hexane 1:2) indicated starting materials remained, so the mixture was warmed to reflux for 4 hours. The reaction was cooled, then partitioned between 30 mL EtOAc and 15 mL of 1 M aqueous Na_2CO_3. The aqueous phase was extracted with 15 mL EtOAc, then the combined organic phases were washed with 20 mL brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to a yellowish oil. Purification by flash chromatography on silica gel eluting with 1:2 Et_2O-hexane gave 19.9 mg (7%) of a less polar product and 20.1 mg (7%) of a more polar product. ^{1}H NMR spectra and MS were the same as those of Example 76B.

Example 77B

(2S,3S,4S)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((1S)-1-(N,N-dipropylaminocarbonyl)-1-butyl)pyrrolidine-3-carboxylic acid

The procedure of Example 73C was followed, with the substitution of the less polar isomer from Example 77A for the resultant product from Example 73B, to provide the title compound in 100% yield. ^{1}H NMR (CD_3OD, 300 MHz) and MS identical to those of Example 75C.

Example 78

(2R,3R,4R)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((1S)-1-(N,N-dipropylaminocarbonyl)-1-butyl)pyrrolidine-3-carboxylic acid

The procedure of Example 73C was followed, with the substitution of the more polar isomer from Example 77A for the resultant product from Example 73B, to provide the title compound in 88% yield. ^{1}H NMR (CD_3OD, 300 MHz) and MS identical to those of Example 76.

Example 79

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-*(N,N-di(n-butyl)aminocarbonylmethyl)*-3-(5-tetrazolyl)pyrrolidine

Carbonyldiimidazole (510 mg, 3.148 mmol) was added to 1.020 g (2.00 mmol) of the compound resulting from Example 43 in 2.7 mL THF, and the mixture was heated for 40 minutes at 50 °C. The reaction mixture was cooled in an ice bath, and 25% solution of ammonia in methanol was added. After 30 minutes, the solid which had formed was filtered,

washed with ethanol and finally with ether to yield 850 mg (83%) of the 3-carboxamide compound. m.p. 194-196 °C.

Phosphorus oxychloride (1.06 g) was added to this amide in 7 mL of pyridine, and the mixture was stirred 1 hour at room temperature. Dichloromethane was added, and the solution was washed with potassium bicarbonate solution, dried over sodium sulfate, and concentrated. The residue was chromatographed on silica gel eluting with 2:1 hexane-ethyl acetate to give 790 mg (96%) of the 3-carbonitrile compound.

To this nitrile in 5 mL toluene was added 385 mg of trimethyl tin chloride and 126 mg sodium azide. The mixture was heated 20 hours at 125 °C (bath temp). After cooling, methanol (5 mL) was added, and the solution was concentrated *in vacuo*. To the resulting residue was added 6 mL of methanol and 6 mL of water containing 0.2 g phosphoric acid. After stirring 1 hour at room temperature, water was added and the mixture extracted with dichloromethane. The combined organic extracts were dried and concentrated, and the resulting residue was crystallized from ether to give a solid. The solid was dissolved in sodium hydroxide solution, filtered from insoluble material and acidified with acetic acid to get 532 mg (62%) of the title compound. m.p. 165-167 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J=7Hz, 3H), 0.87 (t, J=7Hz, 3H), 1.10-1.50 (m, 8H), 3.0-3.6 (m, 8H), 3.70 (s, 3H), 3.7-3.8 (m, 1H), 3.90 (t, J=9Hz, 1H), 4.37 (d, J=9Hz, 1H), 5.86 (s, 2H), 6.62 (d, J=8Hz, 1H), 6.65-6.73 (m, 3H), 6.95 (d, J=2Hz, 1H), 7.11 (d, J=9Hz, 2H).

Example 80

trans,trans-2-(4-Fluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-*(N,N-di(n-butyl)aminocarbonylmethyl)*pyrrolidine-3-carboxylic acid

The title compound was prepared as an amorphous solid from methyl (4-flourobenzoyl) acetate and 5-(2-nitrovinyl)-1,3-benzodioxole using the procedures described in Examples 1 and 43. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, J=7Hz, 3H), 0.90 (t, J=7Hz, 3H), 1.0-1.55 (m, 8H), 2.81 (d, J=13 Hz, 1H), 2.90-3.10 (m, 4H), 3.15-3.30 (m, 1H), 3.32-3.45 (m, 3H), 3.55-3.65 (m, 1H), 3.86 (d, J=10Hz, 1H), 5.94 (dd, J=2Hz, 4Hz, 2H), 6.72 (d, J=8 Hz, 1H), 6.86 (d, J= 8 Hz, 1H), 6.95-7.07 (m, 3H), 7.32-7.45 (m, 2H).

Example 81

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

N,N-Dibutyl glycine (150 mg, 0.813 mmol), prepared by the method of Bowman, R.E., J. Chem. Soc. 1346 (1950), in 0.7 mL of THF was treated with 138 mg (0.852 mmol) carbonyldiimidazole and heated for 30 minutes at 50 °C. After cooling to room temperature, 250 mg (0.678 mmol) of ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-

pyrrolidine-3-carboxylate, the compound resulting from Example 6A, was added, and the mixture was heated at 45 °C for 30 minutes. The product was chromatographed on silica gel, eluting with 1:1 hexane-ethyl acetate to give 306 mg of the intermediate ethyl ester.

The ester was hydrolyzed with sodium hydroxide in water and ethanol to give 265 mg of the title compound as a white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ rotational isomers - 0.75 and 0.85 (2 t, J=7Hz, 3H), 1.05-1.5 (m, 8H), 2.65-3.20 (m, 6H) 3.43-3.70 (m, 3H), 3.72 (s, 3H), 3.87 (d, J=15Hz, 1H), 4.49 (dd, J=12Hz, 6Hz) and 5.23 (dd, J=12Hz, 8Hz) 2H, 5.90 (dd, J=2Hz, 4Hz, 2H), 6.63-6.78 (m, 3H), 6.86 and 7.04 (d, J=9Hz, 2H), 7.22 (d, J=9Hz, 2H).

Example 82

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-n-butyl)-N-(n-propyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The title compound was prepared using the procedures described in Example 1. m.p. 160-162 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) rotational isomers δ 0.69, 0.80, 0.84, 0.87 (four triplets, J=7Hz, 6H), 1.00-1.52 (m, 6H), 2.63 and 2.66 (two doublets, J=13Hz, 1H), 2.90-3.10 (m, 4H), 3.23-3.61 (m, 5H), 3.71 and 3.75 (two doublets, J=10Hz, 1H), 3.78 (s, 3H), 5.92-5.96 (m, 2H), 6.72 (d, J=8Hz, 1H), 6.83-6.89 (m, 3H), 7.03 (d, J=2Hz, 1H), 7.81 (d, J=9Hz, 2H).

Example 83

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N,N-di(n-propyl)aminocarbonyl)ethyl]pyrrolidine-3-carboxylic acid

The compound resulting from Example 6A (250 mg, 0.677 mmol), 205 mg (1.36 mmol) diallyl acrylamide (Polysciences, Inc.), and 10 mg acetic acid were heated at 85 °C in 0.75 mL of methoxyethanol for one hour. Toluene was added, and the solution was washed with bicarbonate solution, dried, and concentrated. Chromatography on silica gel eluting with 3:1 hexane-ethyl acetate gave 283 mg (80%) of the diallyl compound.

The diallyl compound was hydrogenated using 10% Pd/C catalyst (27 mg) in ethyl acetate (25 mL) under a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated to afford the dipropyl amide ethyl ester in 100% yield.

The ester was hydrolyzed to the title compound by the method of Example 1D in 83% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 and 0.83 (two triplets, J=7Hz, 6H), 1.39-1.54 (m, 4H), 2.35-2.60 (m, 3H), 2.80-3.07 (m, 5H), 3.14-3.21 (m, 2H), 3.31-3.38 (m, 1H), 3.51-3.61 (m, 1H), 3.73 (d, J=12H, 1H), 3.75 (s, 3H), 5.94 (s, 2H), 6,71 (d, J=9Hz, 1H), 6.79-6.85 (m, 3H), 7.04 (d, J=2Hz, 1H)< 7.32 (d, J=9Hz, 2H).

Example 84

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Example 8 using dibutyl carbamoyl chloride, prepared by the method of Hoshino *et al.*, Syn. Comm., 17: 1887-1892 (1987), as a starting material. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J=7Hz, 6H), 1.14-1.28 (m, 4H), 1.35-1.48 (m, 4H), 2.81-2.94 (m, 2H), 3.11 (t, J=12Hz, 1H), 3.30-3.41 (m, 2H), 3.59-3.68 (m, 2H), 3.76 (s, 3H), 3.78-3.85 (m, 1H), 5.81 (d, J=9Hz, 1H), 5.94 (s, 2H), 6.73-6.86 (m, 5H), 7.24 (d, J=9Hz, 2H).

Example 85

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-*(N,N-di(n-butyl)aminocarbonylmethyl)*pyrrolidine-3-carboxylic acid sodium salt

Sodium hydroxide (48.2 mg of 98.3% pure, 1.184 mmol) in 2 mL of MeOH was added to the compound resulting from Example 43 (610 mg, 1.196 mmol.) in 5 mL MeOH. The solution was concentrated to dryness, and the resulting powder was stirred with heptane. The heptane was removed *in vacuo* to give a powder which was dried in the vacuum oven for 2 hours at 60 °C to yield 627.5 mg of the title compound.

Example 86

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N,N-di(n-butyl)amino)ethyl]pyrrolidine-3-carboxylic acid

A solution of the bromoethyl compound resulting from Example 61A (150 mg), dibutylamine (150 mg) and sodium iodide (18 mg) in 0.75 mL ethanol was heated at 80 °C for 1 hour. After cooling, toluene was added, and the solution was washed with potassium bicarbonate solution, dried over Na_2SO_4 and concentrated. More toluene was added, and the solution was again concentrated to get rid of excess dibutylamine. The residue was dissolved in warm heptane and filtered from a small amount of insoluble material. The hepane was removed *in vacuo* to give 143 mg (87%) of the intermediate ethyl ester.

The ester was hydrolyzed by the method of Example 1D to give the title compound as a white powder. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (t, J=7Hz, 6H), 1.16-1.30 (m, 4H), 1.44-1.56 (m, 4H), 2.48-2.57 (m, 1H), 2.80-3.08 (m, 8H), 3.14-3.25 (m, 1H), 3.31-3.38 (m, 1H), 3.59-3.60 (m, 1H), 3.74 (s, 3H), 3.75 (d, J=10Hz, 1H), 5.89 (s, 2H), 6.71 (d, J=9Hz, 1H), 6.81 (dd, J=9Hz, 2Hz, 1H), 6.90 (d, J=10Hz, 2H), 6.96 (d, J=2Hz, 1H), 7.37 (d, J=10Hz, 2H).

Example 87

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-{2-[N-(N,N-di(n-butyl)aminocarbonyl)-N-methylamino]ethyl}pyrrolidine-3-carboxylic acid

Dibutyl carbamoyl chloride (135 mg) was added to the compound resulting from Example 61B (250 mg) and 150 mg triethylamine in 1 mL dichloromethane. After stirring 1 hour at room temperature, toluene was added, and the solution was washed with potassium bicarbonate solution, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel, eluting with a mixture of 38% EtOAc and 62% hexane to give 194 mg of the ethyl ester intermediate.

The ester was hydrolyzed by the method of Example 1D to afford 141 mg of the title compound. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.92 (t, J=7Hz, 6H), 1.21-1.32 (m, 4H), 1.42-1.53 (m, 4H), 2.62 (s, 3H), 2.65-2.76 (m, 1H), 3.00-3.20 (m, 8H), 3.44-3.55 (m, 1H), 3.62-3.78 (m, 2H), 3.80 (s, 3H), 4.07 (d, J=12 Hz, 1H), 5.93 (s, 2H), 6.75 (d, J=9Hz, 1H), 6.87 (dd, J=9Hz, 2Hz, 1H), 6.94 (d, J=10 Hz, 2H), 7.04 (d, J=2Hz, 1H), 7.40 (d, J=10Hz, 2H).

Example 88

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-(N-methanesulfonyl)carboxamide

Carbonyldiimidazole (75 mg, 0.463 mmol) was added to 150 mg (0.294 mmol) of the compound resulting from Example 43 in 0.4 mL of tetrahydrofuran, and the solution was stirred at 60 °C for 2 hours. After cooling, 50 mg (0.526 mmol) of methanesulfonamide and 68 mg (0.447 mmol) of DBU in 0.3 mL of THF were added. The mixture was stirred at 45 °C for 2 hours. The solvents were removed *in vacuo*, and the residue was dissolved in water. A few drops of acetic acid were added, and the solution was lyophilized to give 121 mg (70%) of the title compound. m.p. 170-173 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J=7Hz, 3H), 0.88 (t, J=7Hz, 3H), 1.05-1.51 (m, 8H), 2.75-2.86 (m, 2H), 2.83-3.25 (m, 4H), 3.17 (s, 3H), 3.32-3.50 (m, 3H), 3.70-3.78 (m, 1H), 3.80 (s, 3H), 3.87 (d, J=10Hz, 1H), 5.96 (dd, J=2Hz, 4Hz, 2H), 6.74 (d, J=9Hz, 1H), 6.84 (dd, J=9Hz, 2Hz, 1H), 6.90 (d, J=10 Hz, 2H), 7.01 (d, J=2Hz, 1H), 7.34 (d, J=10Hz, 2H).

Example 89

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-(N-benzenesulfonyl)carboxamide

The compound resulting from Example 43 was converted to the title compound by the method of Example 88 substituting benzenesulfonamide for methanesulfonamide. m.p. 169-171 °C for a sample recrystallized from acetonitrile. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81(t, J=7 Hz, 3H), 0.89 (t, J=7Hz, 3H), 1.02-1.50 (m, 8H), 2.65-2.80 (m, 2H), 2.90-3.25 (m, 4H), 3.80-3.95 (m, 3H), 3.50-3.60 (m, 1H), 3.65 (d, J=10Hz, 1H), 3.81 (s, 3H), 5.94 (s, 2H), 6.70

(s, 2H), 6.81-6.90 (m, 3H), 7.17 (d, J=10Hz, 2H), 7.55 (t, J=7 Hz, 2H), 7.66 (t, J=7Hz, 1H), 8.95 (d, J=7Hz, 2H).

Example 90

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-di(n-butyl) aminosulfonylmethyl]-pyrrolidine-3-carboxylic acid

Chloromethyl sulfenyl chloride, prepared by the method of Brintzinger et. al., Chem. Ber. 85: 455-457 (1952), is reacted with dibutylamine by the method of E. Vilsmaier described in Liebigs Ann. Chem. 1055-1063 (1980) to give N,N-dibutyl chloromethyl sulfenyl chloride. Alternatively dimethyl(methylthio)sulfonium tetraflouroborate is reacted with dibutylamine to give N,N-dibutyl methylsulfenyl chloride which is chlorinated with N-chlorosuccinimide to give chloromethyl sulfenyl chloride by the method of E. Vilsmaier, described in the above reference.

The N,N-dibutyl chloromethyl sulfenyl chloride is reacted with the compound resulting from Example 6A to give ethyl *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-di(n-butyl)aminosulfenylmethyl]-pyrrolidine-3-carboxylate. This is oxidized with osmium tetroxide and N-methyl morpholine N-oxide by the method of S. Kaldor and M. Hammond, Tet. Lett. 32: 5043-5045 (1991) to give the title compound after hydrolysis of the ethyl ester.

Example 91

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(N,N-di(n-butyl)aminocarbonyl-1-(*RS*)-ethyl]pyrrolidine-3-carboxylic acid

Example 91A

(±)-Dibutyl 2-bromopropanamide

2-Bromopropanoic acid (510 mg, 3.33 mmol) and 4-methylmorpholine (0.74 mL, 6.73 mmol) were dissolved in 10 mL of CH_2Cl_2, the solution was cooled to 0 °C under a N_2 atmosphere, and then treated dropwise with isobutyl chloroformate (0.45 mL, 3.5 mmol). After 10 minutes at 0 °C, dibutylamine (0.57 mL, 3.4 mmol) was added. The reaction was stirred at 0 °C for 1 hour and for an additional 16 hours at room temperature. The mixture was partitioned with 25 mL of 1.0 M aqueous Na_2CO_3 solution, then the organic phase was washed sequentially with 25 mL of 1 M aqueous $NaHSO_4$ and 25 mL brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 698 mg (2.64 mmol, 79 %) of the crude bromoamide as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J=7Hz) and 0.97 (t, J=7.5Hz, 6H

total), 1.26-1.60 (m, 7H), 1.60-1.78 (m, 1H), 1.82 (d, J=6Hz, 3H), 3.04-3.27 (m, 2H), 3.42-3.64 (m, 2H), 4.54 (q, J=7H, 1H). MS (DCI/NH_3) m/e 264 and 266 $(M+H)^+$.

Example 91B

trans,trans- and *cis,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((N,N-di(n-butyl)amino)carbonyl-1-(*RS*)-ethyl)pyrrolidine-3-carboxylic acid ethyl ester

A solution of the resultant mixture of *trans,trans* and *cis,trans* compounds from Example 1C (232 mg, 0.628 mmol) and the resultant compound from Example 91A (183 mg, 0.693 mmol) in 2 mL of CH_3CN was treated with diisopropylethylamine (0.22 mL, 1.3 mmol). The solution was stirred at 60-80 °C under a N_2 atmosphere for 16 hours. The reaction was concentrated under reduced pressure, then the residue was partitioned between 30 mL Et_2O and 10 mL of 1 M aqueous Na_2CO_3 solution. The organic phase was washed with 20 mL water and 20 mL brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude amino amide as a brown oil (339 mg, 98% crude). The product was obtained by flash chromatography on silica gel eluting with 20% EtOAc-hexane to provide 224 mg (70%) of the title compounds as a mixture of 4 diastereomers. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.66-1.55 (several m, 19H), 2.63-3.00 (m, 3H), 3.05-3.39 (m, 2H), 3.40-3.76 (m, 4H), 3.78-3.80 (4 s, 3H), 3.84-4.25 (m, 2.6H), 4.38 (d, J=10.5Hz, 0.2H) and 4.58 (d, J=10.5Hz, 0.2H), 5.90-5.97 (m, 2H), 6.68-6.96 (m, 5H), 7.38-7.43 (m, 2H). MS (DCI/NH_3) m/e 553 $(M+H)^+$.

Example 91C

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((N,N-dibutylamino)carbonyl-1-(*RS*)-ethyl)pyrrolidine-3-carboxylic acid

The procedure of Example 73C was used, substituting the resultant compound from Example 91B for the resultant compound from Example 73B to give the title compound in 61% yield. ^1H NMR (CD_3OD, 300 MHz) δ 0.70-1.05 (several m, 8H), 1.14 (d, J=6Hz, 2H), 1.17-1.55 (m, 6H), 2.79-3.03 (m, 3.5H), 3.20-3.65 (br m, 4.6H plus CD_2HOD), 3.70-3.78 (m, 0.4H), 3.79 (s, 3H), 3.98 (d, J=8Hz, 0.6H), 4.06 (t, J=7.5Hz, 0.4H), 4.25 (d, J=8Hz, 0.4H), 5.92 (s) and 5.94 (s, 2H total 6H), 6.73 (d, J=2.5Hz) and 6.75 (d, J=3Hz, 1H total), 6.78-6.85 (m, 1H), 6.91-7.00 (m, 3H), 7.30-7.38 (m, 2H). MS (DCI/NH_3) m/e 525 $(M+H)^+$. Anal calcd for $C_{30}H_{40}N_2O_6 \cdot 0.5H_2O$: C, 67.52; H, 7.74; N, 5.25. Found: C, 67.63; H, 7.65; N, 5.21.

Example 92

trans,trans-2-(Pentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 92A

Methyl 2-(4-hexenoyl)-4-nitro-3-(1,3-benzodioxole-5-yl)butyrate

A solution of methyl 3-oxo-6-octenoate (502 mg, 2.95 mmol) in 10 mL of isopropanol was added to a solution of 5-(2-nitrovinyl)-1,3-benzodioxole (712 mg, 3.69 mmol) in 10 mL THF, then DBU (22 μL, 0.15 mmol) was added. The resulting reddish solution was stirred at room temperature for 20 minutes. TLC (ethyl acetate-hexane, 1:3) indicated complete consumption of ketoester. The solution was concentrated *in vacuo* and flash chromatographed on silica gel eluting with 18% ethyl acetate in hexane to produce 879 mg (2.42 mmol, 82%) of the title compound as a mixture of diastereomers in a 1:1 ratio. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55-1.66 (m, 3H), 2.02-2.17 (br m, 1H), 2.20-2.37 (m, 1.5H), 2.49-2.76 (m, 1.5H), 3.57 (s, 1.5H), 3.74 (s, 1.5H), 3.97 (d, J=7.5H, 0.5H) and 4.05 (d, J =8Hz, 0.5H), 4.10-4.20 (m, 1H), 4.68-4.82 (m, 2H), 5.06-5.52 (m, 2H), 5.95 (2s, 2H), 6.65 (m, 1H), 6.68 (br s, 1H), 6.75 (d, 7.5Hz, 1H). MS (DCI/NH_3) m/e 381 $(M+NH_4)^+$. Anal calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.82; N, 3.85. Found: C, 59.32; H, 5.71; N, 3.72.

Example 92B

Methyl *trans,trans*-2-(pentyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylate

The procedures of Example 1B and Example 1C were followed, with the substitution of the resultant compound from Example 92A for the resultant compound from Example 1A, and the substitution of the this resultant compound for the resultant compound from Example 1B, to provide the title compound in crude form as a yellow oil. This crude compound was epimerized under the following conditions. A solution of the crude compound (660 mg, 2.07 mmol) in 3 mL methanol was treated with a solution of sodium methoxide (made by the addition of sodium metal (14 mg, 0.61 mmol) to 1 mL of methanol). The resultant solution was heated at reflux for 18 hours. The reaction was concentrated under reduced pressure, and the residue was partitioned between 25 mL saturated $NaHCO_3$ diluted with 10 mL water and 30 mL of CH_2Cl_2. The aqueous phase was extracted (2 x 30 mL CH_2Cl_2), then the combined organic phases were washed with 20 mL brine, dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel eluting with 3.5% methanol in CH_2Cl_2 gave 336 mg (57%) the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (br t, 3H), 1.25-1.70 (br m, 8H), 1.83-2.02 (br s, 2H), 2.58 (dd, J=8,9Hz, 1H), 2.99 (dd,

J=8,14Hz, 1H), 3.34-3.45 (m, 2H), 3.53 (q, J=9Hz, 1H), 3.66 (s, 3H), 5.94 (s, 2H), 6.65-6.75 (m, 3H). MS (DCI/NH_3) m/e 320 $(M+H)^+$. Anal calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.39; H, 7.84; N, 4.37.

Example 92C

trans,trans-2-(Pentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The procedures of Example 1B-1D were used, with the substitution of the resultant compound from Example 92A for the resultant compound from Example 1B, to provide the title compound as a white foam. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (br t) and 0.89 (br t, 6H total), 0.97 (t, J=7.5Hz, 3H), 1.21-1.42 (br m, 10), 1.43-1.78 (br m, 6H), 2.76 (t, J=7Hz, 1H), 3.02-3.30 (br m, 6H), 3.40-3.60 (m, 3H), 3.73 (d, J=14Hz, 1H), 5.98 (AB, 2H), 6.70 (d, J=7Hz, 1H), 6.77 (dd, J=1.5,7Hz, 1H), 6.89 (d, J=1.5Hz, 1H). MS (DCI/NH_3) m/e 475 $(M+H)^+$. Anal calcd for $C_{27}H_{42}N_2O_5 \cdot 0.5H_2O$: C, 67.05; H, 8.96; N, 5.79. Found: C, 67.30; H, 8.77; N, 5.68.

Example 93

trans,trans-2-(Pentyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-propylsulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

Example 93A

Methyl *trans,trans*-2-(pentyl)-4-(1,3-benzodioxol-5-yl)-1-(2-bromoethyl)pyrrolidine-3-carboxylate

The procedure of Example 61A was used, with the substitution of the resultant compound from Example 92B for the resultant compound from Example 1C, to provide the title compound as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (br t, J=7Hz, 3H), 1.24-1.40 (br m, 6H), 1.60-1.80 (br m, 2H), 2.61-2.75 (m, 2H), 2.76-2.91 (m, 2H), 3.10-3.22 (m, 2H), 3.36-3.47 (m, 2H), 3.68 (s, 3H), 5.92 (s, 2H), 6.69-6.77 (m, 2H), 6.90-6.94 (m, 1H). MS (DCI/NH_3) m/e 426, 428 $(M+H)^+$.

Example 93B

Methyl *trans,trans*-2-(Pentyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-propylsulfonylamino)ethyl]pyrrolidine-3-carboxylate

A solution of the resultant compound from Example 93A (102 mg, 0.24 mmol) and tetrabutylammonium iodide (6 mg, 16 μmol) in 1 mL EtOH was treated with propylamine (60 μL, 0.73 mmol). The solution was warmed to 80 °C for 4 hours. The reaction was concentrated under reduced pressure, then the residue was dissolved

in 35 mL ethyl acetate and extracted with 2 x 15 mL of 1 M aqueous Na_2CO_3. The organic phase was washed with 15 mL brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the crude secondary amine as a yellow oil (94.2 mg). The crude amine was dissolved in 1 mL of CH_2Cl_2, diiosopropylethylamine (65 μL, 0.373 mmol) was added, followed by propylsulfonyl chloride (29 μL, 0.26 mmol). The solution was stirred at room temperature for 4 hours. The reaction was quenched with 10% aqueous citric acid (to pH 4), and the mixture was extracted with 2 x 3 mL CH_2Cl_2. The combined organic extracts were washed with 2 mL brine, then dried over Na_2SO_4, filtered, concentrated *in vacuo*. Purification by flash chromatography eluting with 20% ethyl acetate in hexane provided 65.0 mg (53%) of the title compound as a waxy solid. R_f = 0.17 (20%EtOAc-hexane). MS (DCI/NH_3) m/e 511 $(M+H)^+$.

Example 93C

trans,trans-2-(Pentyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-propylsulfonylamino)ethyl]pyrrolidine-3-carboxylic acid

The procedure of Example 71C was followed, with the substitution of the resultant compound from Example 93B for the resultant compound from Example 71B, to provide the title compound as a white foam (47 mg, 80%), R_f = 0.14 (5%MeOH-CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (br t) and 0.92 (t, J=7Hz, 6H total), 1.22-1.52 (br m, 6H), 1.63 (sextet, J=8Hz, 2H), 1.75-2.10 (br m, 4H), 2.89-2.98 (m, 2H), 3.05 (br t, J=9Hz, 1H), 3.10-3.30 (m, 3H), 3.30-3.80 (br m, 7H), 5.94 (s, 2H), 6.71 (t, J=8Hz, 1H), 6.77 (dd, J=1.5,8Hz, 1H), 6.89 (d, J=1.5Hz, 1H). MS (DCI/NH_3) m/e 497 $(M+H)^+$.

Example 94

trans,trans-2-(Propyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 94A

Ethyl 2-(4-butanoyl)-4-nitro-3-(1,3-benzodioxole-5-yl)butyrate

The procedure of Example 92A was followed, with the substitution of ethyl butyryl acetate for methyl 3-oxo-6-octenoate, to provide the title compound as a mixture of *trans* and *cis* isomers (47 mg, 80%), R_f = 0.28 (25%EtOAc-hexane). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.74 (t, J=7.5Hz) and 0.91 (t, J=7.5Hz, 3H total), 1.08 (t, J=7Hz) and 1.28 (t, J=7Hz, 3H total), 1.45 (sextet, J=7Hz, 1.5H), 1.63 (sextet, J=7Hz, approx. 1.5H), 2.17 (t, J=7Hz) and 2.24 (t, J=7Hz, 0.5H total)2.40-2.54 (m, 1H), 2.60

(t, J=7.5Hz) and 2.67 (t, J=7.5Hz, 0.5H total), 3.93-4.09 (m, 2H), 4.10-4.20 (br m, 1H), 4.23 (q, J=7Hz, 1H), 4.67-4.85 9m, 2H), 5.94 (s, 2H), 6.62-6.75 (m, 3H). MS (DCI/NH_3) m/e 369 $(M+NH_4)^+$. Anal calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.21; H, 5.98; N, 3.81.

Example 94B

Ethyl *trans,trans*-2-(propyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylate

The procedure of Example 92B was followed, with the substitution of the resultant compound from Example 94A for the resultant compound from Example 92A, to afford the title compound. MS (DCI/NH_3) m/e 306 $(M+H)^+$.

Example 94C

trans,trans-2-(Propyl)-4-(1,3-benzodioxol-5-yl)-1-((N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The procedure of Example 92C was followed, with the substitution of the resultant product from Example 94B for the resultant product from Example 92B, to give the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J=7.5Hz), 0.92 (t, J=7.5Hz), and 0.97 (t, J=7.5H, 9H total), 1.22-1.80 (br m, 12H), 2.83 (t, J=7.5Hz, 1H), 3.40-3.55 (br m, 2H), 3.55-3.68 (m, 1H), 3.78 (d, J=15Hz, 1H), 5.92 (q, J=1Hz, 2H), 6.70 (d, J=8Hz, 1H), 6.79 (dd, J=1Hz,8Hz, 1H), 6.90 (d, J=1Hz, H). MS (DCI/NH_3) m/e 447 $(M+H)^+$. Anal calcd for $C_{25}H_{38}N_2O_5 \cdot 0.5\ H_2O$: C, 65.91; H, 8.63; N, 6.15. Found: C, 65.91; H, 8.68; N, 5.94.

Example 95

(2R,3R,4S)-(+)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(tert-butyloxycarbonyl-aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Example 95A

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-([tert-butyloxycarbonylaminocarbonylmethyl]pyrrolidine-3-carboxylic acid

The resulting mixture of 64% *trans,trans*- and *cis,trans*- pyrrolidines resulting from Example 1C (3.01 g, 8.15 mmol) was dissolved in 50 mL of methylene chloride. To this was added dropwise a solution of di-tert-butyl dicarbonate (1.96 g, 8.97 mmol) in 20 mL methylene chloride under a nitrogen atmosphere, and the resulting solution was stirred 30 minutes at which point TLC (ethyl acetate:hexane, 1:1) indicated that all of the starting material was consumed. The reaction mixture was concentrated and dried under high vacuum to give 3.94 g of the ethyl ester as a yellow-brown oil. ^1H NMR ($CDCL_3$, 300 MHz) δ 0.99,

1.07 (br t, br t, J=7 Hz, 3H), 1.11-1.62 (several br m, 9H), 3.05 (br m, 1H), 3.44-3.95 (m, 3H), 3.81 (s, 3H), 4.04 (q, J=7 Hz, 1H), 4.14-4.28 (br m, 1H), 4.89-5.24 (br m, 1H), 5.94 (d, J=3 Hz, 2H), 6.69-6.90 (m, 5H), 7.06-7.20 (m, 2H). MS (DCI/NH_3) m/e 470 $(M+H)^+$.

To the ethyl ester dissolved in 170 mL of ethanol was added a solution of lithium hydroxide (1.06 g, 25.17 mmol) in 60 mL of water. The reaction mixture was vigorously stirred for 18 hours under a nitrogen atmosphere. The reaction mixture was concentrated to remove ethanol, diluted with 250 mL of water and extracted three times with 250 mL of ether. The organic phase acidified to slight cloudiness (pH ~7) with 1 N hydrochloric acid, then to pH 4 with 10 % citric acid and extracted with 5 % ethanol in methylene chloride (3 x 100 mL). The combined organic layers dried (Na_2SO_4), filtered, concentrated and dried on high vacuum to give the title compound as a white foam (2.19 g, 60 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (v br s, 9H), 3.11 (br m, 1H), 3.50-3.64 (m, 2H), 3.81 (s, 3H), 4.24 (br m, 1H), 4.96 (br m, 1H), 5.94 (s, 2H), 6.71-6.79 (m, 3H), 6.84-6.91 (m, 2H), 7.19 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/e 442 $(M+H)^+$.

Example 95B

(2R,3R,4S)-(+)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(tert-butyloxycarbonylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The compound resulting from Example 95A (2.15 g, 4.86 mmol) and (+)-cinchonine (1.43 g, 4.86 mmol) were added to 100 mL of methylene chloride; this suspension was swirled with warming as necessary to get all solids to dissolve. The solution was then concentrated and dried on high vacuum to a white foam. This material was crystallized from a mixture of refluxing chloroform (64 mL) and hexane (360 mL). The resulting crystals were isolated by filtration and recrystallized under the same conditions seven additional times. Each time the resulting crystals and filtrate were monitored by ^{1}H NMR and chiral HPLC. The amount of (2S,3S,4R)-(-)- enantiomer decreased first in the crystals and then in the filtrate with the predetermined endpoint achieved when the (2S,3S,4R)-(-)- enantiomer could no longer be detected in the filtrate. The pure (2R,3R,4S)-(+)- enantiomer thus obtained was partitioned between 100 mL of 10% citric acid and 100 mL of ether. The aqueous layer was further extracted twice with 100 mL of ether. The combined ether layers were washed with brine, dried (Na_2SO_4), filtered, concentrated and dried on high vacuum to a white powder (550 mg, 55 % of theoretical 50 % maximum, >99.5 ee). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05-1.50 (br m, 9H), 3.12 (br m, 1H), 3.50-3.65 (m, 2H), 3.81 (s, 3H), 4.24 (m, 1H), 4.96 (br m, 1H), 5.95 (s, 2H), 6.70-6.79 (m, 3H), 6.86 (d, J=9 Hz, 2H), 7.19 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/e 442 $(M+H)^+$.

Example 95C

(2R,3R,4S)-(+)-Ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate

The compound resulting from Example 95B (251 mg, 0.568 mmol) was dissolved in 20 mL of a saturated solution of anhydrous HCl(g) in anhydrous ethanol. The resulting solution was heated at 50 °C. with stirring for 18 hours at which point all of the precipitated solid had dissolved. The reaction mixture was concentrated to a solid which was partitioned between O.8 M aqueous sodium carbonate (50 mL) and methylene chloride (50 mL). The aqueous layer was further extracted with methylene chloride (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated and dried under high vacuum to give the title compound as an almost colorless oil (158 mg, 69%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.11 (t, J=7 Hz, 3H), 2.18 (v br s, 1H), 2.93 (t, J= 9 Hz, 1H), 3.19,3.22 (dd, J=7 Hz, 1H), 3.50-3.69 (m, 2H), 3.80 (s, 3H), 4.07 (q, J=7 Hz, 2H), 4.49 (d, J=9 Hz, 1H), 5.94 (s, 2H), 6.73 (d, J=2 Hz, 2H), 6.81-6.92 (m, 3H), 7.34-7.41 (m, 2H). MS (DCI/NH_3) m/e 370 $(M+H)^+$.

Example 95D

(2R,3R,4S)-(+)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(tert-butyloxycarbonyl-aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

To the resulting compound from Example 95C (131 mg, 0.355 mmol) was added, diisopropylethylamine (137 mg, 185 µL, 1.06 mmol), acetonitrile (2 mL), N,N-di-(n-butyl)bromoacetamide (133 mg, 0.531 mmol), and the mixture was heated at 50 °C. for 1.5 hours. The reaction mixture was concentrated to a solid, dried under high vacuum, and purified by chromatography on silica gel eluting with 1:3 ethyl acetate-hexane to give pure ester as a colorless oil. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.81 (t, J=7 Hz, 3H), 0.88 (t, J=7 Hz, 3H), 1.10 (t, J=7 Hz, 3H), 1.00-1.52 (m, 8H), 2.78 (d, J=14 Hz, 1H), 2.89-3.10 (m, 4H), 3.23-3.61 (m, 5H), 3.71 (d, J=9 Hz, 1H), 3.80 (s, 3H), 4.04 (q, J=7 Hz, 2H), 5.94 (dd, J=1.5 Hz, 2H), 6.74 (d, J=9 Hz, 1H), 6.83-6.90 (m, 3H), 7.03 (d, J=2 Hz, 1H), 7.30 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/e 539 $(M+H)^+$.

To the ethyl ester dissolved in 7 mL of ethanol was added a solution of lithium hydroxide (45 mg, 1.06 mmol) in water (2.5 mL). The mixture was stirred for 1 hour at ambient temperature and then warmed slowly to 40 °C. over 2.5 hours at which point all of the starting material had been consumed. The reaction mixture was concentrated to remove the ethanol, diluted with 60 mL water and extracted with ether (3 x 40 mL). The aqueous solution was treated with 1 N aqueous hydrochloric acid until cloudy, and the pH was then adjusted to ~4-5 with 10% aqueous citric acid. This mixture was extracted with 1:19 ethanol-methylene chloride (3 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered, concentrated and dried under high vacuum to give the title compound as a white foam (150

mg, 83%). ^1H NMR ($CDCl_3$, 300MHz) δ 0.80 (t, J=7 Hz, 3H), 0.88 (t, J=7 Hz, 3H), 1.08 (m, 2H), 1.28 (m, 3H), 1.44 (m, 3H), 2.70-3.77 (svr br m, 12H), 3.79 (s, 3H), 5.95 (m, 2H), 6.75 (d, J=8 Hz, 1H), 6.87 (br d, J=8 Hz, 3H), 7.05 (br s, 1H), 7.33 (v br s, 2H). MS (DCI/NH_3) m/e 511 $(M+H)^+$. $[\alpha]^{22}$ = +74.42°. Anal calcd for $C_{29}H_{38}N_2O_6 \cdot 0.5\ H_2O$: C ,67.03; H, 7.56; N, 5.39. Found: C, 67.03; H, 7.59; N, 5.33.

Example 95E

Alternate Preparation of (2R,3R,4S)-(+)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(tert-butyloxycarbonylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The product of Example 95A (2.858 g) was suspended in 10 mL of EtOAc. 0.7833 g of R (+) alpha methyl benzylamine in 3 mL ethyl acetate was added. On swirling all of the solids were dissolved. The ethyl acetate was removed in vacuum. Ether (13 ml) was added to the residue. When all of the residue had dissolved, 5 mg of seed crystals were added and these crystals were crushed with a metal spatula while cooling in ice. The product crystallized very slowly. After 1 hour the solid was filtered and washed with ether giving 1.4213 g, m.p. 163-167°. The filtrate was concentrated, cooled and scratched with a spatula to give a second crop 0.1313 g, m.p. 164-168°. The filtrate was concentrated again and put in the refrigerator and let stand overnight giving 1.6906 g, m.p. 102-110°. (HPLC of this showed 20%of the desired enantiomer and 80% of the unwanted enantiomer.)

The first two batches of crystallized material were combined and suspended in 20 mL dichloromethane (Note: the unwanted isomer is more soluble in dichloromethane) and stirred for 2 minutes. The mixture was concentrated, but not to dryness, and ether (10 mL) was added. After stirring for a few minutes the crystals were filtered. Yield: 1.401 g, m.p. 164-172°.

Treatment of the crystalline product with 10% citric acid and ether according the method described in Example 95B provided the title compound.

Example 96

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-butyrylamino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and butyryl chloride for isobutyryl chloride in Example 61C. The product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (m, 3H), 0.90 (t, 3H, J=8Hz), 1.42 (m, 2H), 1.58 (heptet, 2H, J=8Hz), 2.20 (t, 3H, J=8Hz), 2.94 (br m,

2H), 3.10 (br m, 2H), 3.48 (br m, 4H), 3.76 (br m, 2H), 3.78 (s, 3H), 4.30 (br s, 1H), 5.95 (s, 2H), 6.75 (d, 1H, J=8Hz), 6.84 (m, 1H), 6.85 (d, 2H, J=8Hz), 7.04 (d, 1H, J=1Hz), 7.40 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 497 $(M+H)^+$. Anal calcd for $C_{28}H_{36}N_2O_6 \cdot 1.0$ TFA: C, 58.82; H, 6.42; N, 4.57. Found: C, 58.77; H, 6.30; N, 4.42.

Example 97

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(ethylaminocarbonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and ethyl isocyanate for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether-hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 0.80 (t, J=8Hz) and 1.05 (t, J=8Hz) and 1.20 (m) and 1.42 (m) total of 8H for the four peaks, 2.35 (br s, 1H), 2.70 (m, 1H), 3.0 (m, 3H), 3.2 (m, 3H), 3.25 (dq, 1H, J=1,8Hz), 3.42 (m, 1H), 3.6 (m, 1H), 3.75 (m, 1H), 3.78 (s, 3H), 4.8 (br s, 1H), 5.95 (s, 2H), 6.74 (d, 1H, J=8Hz), 6.85 (m, 3H), 7.00 (s, 1H), 7.30 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 498 $(M+H)^+$. Anal calcd for $C_{27}H_{35}N_3O_6 \cdot 0.75\ H_2O$: C, 63.45; H, 7.20; N, 8.22. Found: C, 63.38; H, 7.29; N, 8.44.

Example 98

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-butyl-N-butyrylamino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting butylamine for methylamine in Example 61B and butyryl chloride for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether-hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (m, 3H), 0.90 (t, 3H, J=8Hz), 1.45 (m, 4H), 1.6 (m, 2H), 2.20 (t, 3H, J=8Hz), 2.94 (br m, 2H), 3.10 (br m, 2H), 3.5 (br m, 4H), 3.80 (br m, 2H), 3.82 (s, 3H), 4.30 (br s, 1H), 5.95 (s, 2H), 6.75 (d, 1H, J=8Hz), 6.84 (m, 1H), 6.85 (d, 2H, J=8Hz), 7.04 (d, 1H, J=1Hz), 7.40 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 511 $(M+H)^+$. HRMS calcd for $C_{29}H_{38}N_2O_6$: 511.2808. Found: 511.2809

Example 99

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-ethoxycarbonylamino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and ethyl chloroformate for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1

diethyl ether-hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3H, J=8Hz), 1.05 (m, 2H), 1.22 (m, 3H), 1.45 (m, 3H), 2.08 (br s, 1H), 2.75 (m, 1H), 2.88 (br q, 2H, J=8Hz), 3.08 (br m, 2H), 3.27 (br m, 2H), 3.44 (m, 1H), 3.54 (dt, 1H, J=1,8Hz), 3.63 (d, 1H, J=8Hz), 3.78 (s, 3H), 4.02 (br d, 2H), 5.93 (s, 2H), 6.72 (d, 1H, J=8Hz), 6.81 (dd, 1H, J=1,8Hz), 6.85 (d, 2H, J=8Hz), 7.00 (s, 1H), 7.30 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 499 $(M+H)^+$. Anal calcd for $C_{27}H_{34}N_2O_7 \cdot 0.5\ H_2O$: C, 63.89; H, 6.95; N, 5.52. Found: C, 64.03; H, 6.71; N, 5.30.

Example 100

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-methyl-N-(2-ethylbutyryl)amino)ethyl]pyrrolidine-3-carboxylic acid

To the compound resulting from Example 61B (190 mg) dissolved in THF (2 mL) was added HOBt (60 mg), EDCI (85 mg), N-methylmorpholine (50 µL), and DMF (2 mL). 2-Ethylbutyric acid was added and the solution stirred overnight at ambient temperature. Water (10 mL) was added, and the mixture was extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution, 1 N H_3PO_4, and brine, dried with Na_2SO_4, and evaporated to give an oil which was purified by flash chromatography on silica gel eluting with 1:3 EtOAc-hexane. The resulting ethyl ester was saponified by the procedure described in Example 61C. The crude product was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) (mixture of rotamers) δ 0.66, 0.74, 0.80, 0.88 (all triplets, total of 6H, J=8Hz), 1.05 (m, 2H), 1.25-1.75 (m, 5H), 2.16 (m, 1H), 2.32 (m, 1H), 2.45 (m, 1H), 2.70 (m, 1H), 2.86, 2.94 (s, total 3H), 2.95 (m, 1H), 3.35 (m, 1H), 3.52 (m, 2H), 3.65 (m, 1H), 3.80 (s, 3H), 5.94, 5.96 (s, total 2H), 6.73 (m, 1H), 6.84 (m, 3H), 6.97 (m, 1H), 7.30 (m, 2H). MS (DCI/NH_3) m/e 497 $(M+H)^+$. Anal calcd for $C_{28}H_{36}N_2O_6 \cdot 0.25\ H_2O$: C, 67.11; H, 7.34; N, 5.59. Found: C, 67.13; H, 7.24; N, 5.56.

Example 101

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-methyl-N-(2-propylvaleryl)amino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedure described in Example 100, but substituting 2-propylpentanoic acid for 2-ethylbutyric acid. The crude product was purified by preparative HPLC (Vydac µC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, 3H, J=8Hz), 0.82 (t, 3H, J=8Hz), 1.10 (m, 4H), 1.2-1.5 (m, 4H), 2.55 (m, 1H), 2.96 (s, 3H), 3.15 (br m, 1H), 3.32 (br m, 1H), 3.56 (m, 2H), 3.68 (m, 1H) 3.68 (s, 3H), 3.70 (m, 1H), 3.80 (m, 2H), 4.65 (br d, 1H), 5.92 (s, 2H), 6.75 (d, 1H, J=8Hz), 6.84 (m, 1H), 6.85 (d, 2H, J=8Hz), 7.05 (s, 1H), 7.42 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 525 $(M+H)^+$. Anal calcd for $C_{30}H_{40}N_2O_6 \cdot 1.25$ TFA: C, 58.51; H, 6.23; N, 4.20. Found: C, 58.52; H, 6.28; N, 4.33.

Example 102

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(tert-butyloxycarbonylmethyl)amino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and t-butyl bromoacetate for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether-hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, 3H, J=8Hz), 1.18 (m, 2H), 1.19 (s, 9H), 2.12 (m, 1H), 2.46 (m, 2H), 2.70 (m, 3H), 2.85 (m, 2H), 3.20 (s, 2H), 3.40 (dd, 1H, J=2,8Hz), 3.50 (dt, 1H, J=2,8Hz), 3.62 (d, 1H, J=8Hz), 3.78 (s, 3H), 5.95 (s, 2H), 6.72 (d, 1H, J=8Hz), 6.84 (m, 1H), 6.85 (d, 2H, J=8Hz), 7.05 (s, 1H), 7.16 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 541 $(M+H)^+$. Anal calcd for $C_{30}H_{40}N_2O_7 \cdot 1.0\ H_2O$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.75; H, 7.35; N, 4.86.

Example 103

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(n-propylaminocarbonylmethyl)amino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and N-propyl bromoacetamide for isobutyryl chloride in Example 61C. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, 3H, J=8Hz), 0.88 (t, 3H, J=8Hz), 1.45 (m, 2H), 1.48 (m, 3H, J=8Hz), 2.55-2.7 (m, 2H), 2.90 (m, 1H), 3.04 (m, 1H), 3.15 (m, 3H), 3.28 (t, 1H, J=8Hz), 3.45 (t, 1H, J=8Hz), 3.60 (m, 2H), 3.70 (d, 2H, J=8Hz), 3.75 (m, 1H), 3.80 (s, 3H), 4.25 (d, 1H, J=8Hz), 5.95 (s, 2H), 6.75(d, 1H, J=8Hz), 6.86 (dt, 1H, J=1,8Hz), 6.88 (d, 2H, J=8Hz), 7.04 (d, 1H, J=1Hz), 7.40 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 526 $(M+H)^+$. Anal calcd for $C_{29}H_{39}N_3O_6 \cdot 1.85$ TFA: C, 53.32; H, 5.59; N, 5.70. Found: C, 53.45; H, 5.62; N, 5.63.

Example 104

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(4-methoxyphenoxycarbonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and 4-methoxyphenylchloroformate for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether-hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) mixture of rotamers δ 0.88 (m,3H), 1.57 (m, 2H), 2.45 (br s) and 2.60 (br s, total of 1H), 2.90-3.15 (m, 4H), 3.42-3.7 (m, 5H), 3.78 (s, 3H), 3.80 (s, 3H), 3.85 (m) and 4.0 (m, total of 1H), 5.95 (s) and 5.98 (s, total of 2H), 6.63(m, 1H), 6.72 (d, 1H, J=8Hz), 6.81 (m,

2H), 6.93 (m, 5H), 7.40 (m, 2H). MS (DCI/NH_3) m/e 577 $(M+H)^+$. Anal calcd for $C_{32}H_{36}N_2O_8 \cdot 1.0\ H_2O$: C, 64.63; H, 6.44; N, 4.71. Found: C, 64.70; H, 6.38; N, 4.63.

Example 105

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(4-methoxybenzoyl)amino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and anisoyl chloride for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether-hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 0.78 (m) and 0.98 (t, J=8Hz) total of 3H, 1.47 (m) and 1.52 (q, J=8Hz) total of 2H, 2.25 (br s, 1H), 2.78 (br s, 1H), 2.90 (br t, 2H), 3.12-3.68 (m, 7H), 3.80 (s, 3H), 3.82 (s, 3H), 5.94 (s, 2H), 6.75(d, 1H, J=8Hz), 6.83 (m, 5H), 6.94 (m, 1H), 7.22 (m, 4H). MS (FAB) m/e 561 $(M+H)^+$. Anal calcd for $C_{32}H_{36}N_2O_7 \cdot 0.75\ H_2O$: C, 66.94; H, 6.58; N, 4.88. Found: C, 67.00; H, 6.38; N, 4.59.

Example 106

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-benzoylamino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and benzoyl chloride for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether-hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) mixture of rotamers δ 0.65 and 0.9 (m, total of 3H) , 1.4 and 1.55 (m, total of 2H), 2.05 and 2.15 (m, total of 1H), 2.6 - 3.6 (m, 8H), 5.92 (s, 2H), 6.70(d, 1H, J=8Hz), 6.82 (m, 4H), 7.2 - 7.4 (m, 6H). MS (DCI/NH_3) m/e 531 $(M+H)^+$. Anal calcd for $C_{31}H_{34}N_2O_6 \cdot 0.3\ H_2O$: C, 69.46; H, 6.51; N, 5.23. Found: C, 69.48; H, 6.19; N, 4.84.

Example 107

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-benzyloxycarbonylamino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and benzyl chloroformate for isobutyryl chloride in Example 61C. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.8 (m,

3H) 1.45 (m, 2H), 2.20 (br m, 1H), 2.75 (m, 1H), 2.93 (m, 1H), 3.15 (m, 2H), 3.32 (m, 3H), 3.52 (m, 2H), 3.66 (m, 1H), 3.78 (s, 3H), 5.00 (m, 2H), 5.94 (s, 2H), 6.72(d, 1H, J=8Hz), 6.82 (m, 3H), 7.0 (br d, 1H, J= 15Hz), 7.2 (s, 4H), 7.30 (m, 3H). MS (FAB) m/e 561 $(M+H)^+$. Anal calcd for $C_{32}H_{36}N_2O_7 \cdot 1.0$ TFA: C, 60.53; H, 5.53; N, 4.15. Found: C, 60.66; H, 5.34; N, 4.28.

Example 108

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(4-methoxybenzyloxycarbonyl)amino)ethyl]pyrrolidine-3-carboxylic acid

The title compound is prepared by the methods described in Example 61, substituting propylamine for methylamine in Example 61B and 4-methoxybenzyl chloroformate for isobutyryl chloride in Example 61C.

Example 109

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-butyl-N-ethoxycarbonylamino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting butylamine for methylamine in Example 61B and ethyl chloroformate for isobutyryl chloride in Example 61C. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, 3H, J=8Hz), 1.20 (m, 5H), 1.34 (m, 2H), 3.08 (m, 2H), 3.17 (m, 2H), 3.52 (m, 2H), 3.75 (m, 2H), 3.78 (s, 3H), 4.06 (q, 2H, J=8Hz), 4.35 (br s, 1H), 5.94 (s, 2H), 6.76 (d, 1H, J=8Hz), 6.92 (d, 2H, J=8Hz), 7.03 (br s, 1H), 7.17 (br s, 1H), 7.7 (br s, 2H). MS (FAB) m/e 513 $(M+H)^+$. Anal calcd for $C_{28}H_{36}N_2O_7 \cdot 0.5$ TFA: C, 61.15; H, 6.46; N, 4.92. Found: C, 60.99; H, 6.80; N, 4.93.

Example 110

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-butyl-N-propoxycarbonylamino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting butylamine for methylamine in Example 61B and propyl chloroformate for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether-hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (br s, 1H), 0.85 (t, 3H, J=8Hz), 0.92 (br s, 1H), 1.22 (m, 3H), 1.40 (m, 3H), 1.62 (br m, 1H), 2.15 (br s, 1H), 2.72 (m, 1H), 2.87 (m, 1H), 3.1-3.45 (m, 5H), 3.55 (m, 1H), 3.64 (d, 1H, J=8Hz), 3.79 (s, 3H), 3.88

(br s, 1H), 3.97 (br s, 1H), 5.95 (s, 2H), 6.73(d, 1H, J=8Hz), 6.85 (m, 3H, 7.0 (s, 1H), 7.30 (d, 2H, J=8Hz). MS (FAB) m/e 527 $(M+H)^+$. Anal calcd for $C_{29}H_{38}N_2O_7 \cdot 0.15\ H_2O$: C, 65.80; H, 7.29; N, 5.29. Found: C, 65.79; H, 7.30; N, 5.21.

Example 111

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-propoxycarbonylamino)ethyl]pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods described in Example 61, but substituting propylamine for methylamine in Example 61B and propyl chloroformate for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether-hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3H, J=8Hz), 093 (m, 3H), 1.43 (m, 3H), 1.62 (m, 1H), 2.15 (br s, 1H), 2.68-3.45 (m, 8H), 3.54 (m, 1H), 3.66 (m, 1H), 3.78 (s, 3H), 3.94 (m, 2H), 5.94 (s, 2H), 6.72 (d, 1H, J=8Hz), 6.82 (m, 1H), 6.84 (d, 2H, J=8Hz), 7.00 (br s, 1H), 7.33 (m, 2H). MS (DCI/NH_3) m/e 513 $(M+H)^+$. Anal calcd for $C_{28}H_{36}N_2O_7 \cdot 0.15\ H_2O$: C, 65.26; H, 7.10; N, 5.44. Found: C, 65.22; H, 6.74; N, 5.06.

Example 112

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2,4-di(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Ethyl (3,4-methylenedioxybenzoyl)acetate, prepared by the method of Krapcho *et al.*, Org. Syn. 47, 20 (1967) starting with 3,4-methylenedioxyacetophenone instead of 4-methoxyacetophenone, was reacted by the procedures described in Example 1 to give the title compound as a white solid. m.p. 58-60 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (quintet, J=6Hz, 6H), 1.12 (sextet, J=6Hz, 2H), 1.24-1.51 (m, 6H), 2.80 (d, J=13Hz, 1H), 2.94-3.12 (m, 4H), 3.28-3.50 (m, 4H), 3.58-3.62 (m, 1H), 3.78 (d, J=9Hz, 1H), 5.95 (s, 4H), 6.73 (dd, J=8Hz, 3Hz, 2H), 6.84-6.89 (m, 2H), 6.92 (d, J=1Hz, 1H), 7.01 (d, H=1Hz, 1H). MS (DCI/NH_3) m/e 525 $(M+H)^+$.

Example 113

trans,trans-1-(2-(N-(n-Butyl)-N-propylsulfonylamino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 64-65 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, J=7Hz, 3H), 0.98 (t, J=7Hz, 3H), 1.12-1.25 (m, 2H), 1.32-1.41 (m, 2H), 1.75 (sextet, J=7Hz, 2H), 2.23-2.31 (m, 2H), 2.72-3.32 (m, 8H), 3.43 (dd, J=9Hz, 3Hz, 1H), 3.53-3.59 (m, 1H), 3.65 (d, J=9Hz, 1H),

3.80 (s, 3H), 5.95 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.83 (dd, J=8Hz, 1Hz, 1H), 6.88 (d, J=9Hz, 2H), 7.02 (d, J=1Hz, 1H), 7.33 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 547 $(M+H)^+$.

Example 114

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Examples 28 and 43, the title compound was prepared as a white solid. m.p. 74-76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J=6Hz, 3H), 0.88 (t, J=8Hz, 3H), 1.08 (sextet, J=8Hz, 2H), 1.21-1.48 (m, 6H), 2.75 (d, J=12Hz, 1H), 2.95-3.09 (m, 4H), 3.26-3.59 (m, 5H), 3.75 (d, J=9Hz, 1H), 3.79 (s, 3H), 4.28 (s, 4H), 6.78 (d, J=9Hz, 1H), 6.85 (d, J=9Hz, 2H), 6.91 (d,d, J=3Hz, 9Hz, 1H), 6.98 (d, J=3Hz, 1H), 7.32 (d, J=9Hz, 2H). MS (DCI/NH_3) m/e 525 $(M+H)^+$.

Example 115

trans,trans-1-(2-(N-Propyl-N-propylsulfonylamino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 72-73 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J=8Hz, 3H), 0.98 (t, J=8Hz, 3H), 1.43 (sextet, J=8Hz, 2H), 1.75 (sextet, J=8Hz, 2H), 2.22-2.32 (m, 1H), 2.69-3.32 (m, 9H), 3.42 (dd, J=3Hz, 12Hz, 1H), 3.52-3.58 (m, 1H), 3.64 (d, J=12Hz, 1H), 3.80 (s, 3H), 5.95 (s, 2H), 6.73 (d, J=11Hz, 1H), 6.83 (dd, J=1Hz, 11Hz, 1H), 6.87 (d, J=11Hz, 2H), 7.0 (d, J=2Hz, 1H), 7.32 (d, J=11Hz, 2H). MS (DCI/NH_3) m/e 533 $(M+H)^+$.

Example 116

trans,trans-1-(2-(N-Butyl-N-butylsulfonylamino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 62-63 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J=6Hz, 3H), 0.91)t, J=6Hz, 3H), 1.20 (sextet, J=6Hz, 2H), 1.33-1.42 (m, 4H), 1.68 (quintet, J=6Hz, 3H),2.23-2.32 (m, 1H), 2.70-3.28 (m, 9H), 3.41 (d, J=8Hz, 1H), 3.52-3.58 (m, 1H), 3.65 (d, J=8Hz, 1H), 3.79 (s, 3H), 5.95 (s, 2H), 6.72 (d, J=8Hz, 1H), 6.82 (d, J=8Hz, 1H), 6.87 (d, J=8Hz, 2H), 7.01 (s, 1H), 7.32 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 561 $(M+H)^+$.

Example 117

trans,trans-1-(2-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxymethoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

4-Hydroxyacetophenone was treated with chloromethyl methyl ether and triethylamine in THF at room temperature to give ethyl 4-methoxymethoxybenzoylacetate which was treated by the procedures described in Example 1 to afford the title compound as a white solid. m.p. 48-49 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, J=7Hz, 3H), 0.88 (t, J=7Hz, 3H), 1.06 (sextet, J=7Hz, 2H), 1.20-1.35 (m, 4H), 1.44 (quintet, J=7Hz, 2H), 2.75 (d, J=12Hz, 1H), 2.94-3.10 (m, 4H), 3.25-3.35 (m, 1H), 3.40 (d, J=12Hz, 1H), 3.43-3.52 (m, 2H), 3.47 (s, 3H), 3.55-3.62 (m, 1H), 3.77 (d, J=9Hz, 1H), 5.15 (s, 2H), 5.94 (m, 2H), 6.73 (d, J=8Hz, 1H), 6.86 (dd, J=1Hz, 8Hz, 1H), 7.0 (d, J=8Hz, 2H), 7.04 (d, J=1Hz, 1H), 7.32 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 541 $(M+H)^+$.

Example 118

trans,trans-1-(2-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-hydroxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid hydrochloride salt

The compound resulting from Example 116 was treated with concentrated HCl in 1:1 THF-isopropanol to give the title compound as a white solid. m.p. 211-212 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.90 (t, J=8Hz, 6H), 1.12-1.27 (m, 6H), 1.36-1.45 (m, 2H), 3.04 (bs, 1H), 3.14-3.35 (t, J=9Hz, 1H), 3.90 (bs, 3H), 4.17 (d, J=15Hz, 1H), 5.96 (s, 2H), 6.82-6.93 (m, 4H), 7.03 (d, J=1Hz, 1H), 7.42 (bs, 2H). MS (DCI/NH_3) m/e 497 $(M+H)^+$.

Example 119

trans,trans-1-(2-(N-Isobutyl-N-propylsulfonylamino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 73-74 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (d, J=6Hz, 6H), 0.98 (t, J=8Hz, 3H), 1.62 (sextet, J=6Hz, 1H), 1.74 (sextet, J=8Hz, 2H), 2.23-2.34 (m, 1H), 2.68-2.98 (m, 7H), 3.08-3.18 (m, 1H), 3.26-3.42 (m, 2H), 3.52-3.58 (m, 1H), 3.65 (d, J=9Hz, 1H), 3.80 (s, 3H), 5.90 (s, 2H), 6.74 (d, J=8Hz, 1H), 6.82 (d, J=8Hz, 1H), 6.86 (d, J=8Hz, 2H), 6.98 (d, J=1Hz, 1H), 7.33 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 547 $(M+H)^+$.

Example 120

trans,trans-1-(2-(N-Benzenesulfonyl-N-propylamino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 89-91 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.74 (t, J=6Hz, 3H), 1.33 (sextet, J=6Hz, 2H), 2.20-2.30 (m, 1H), 2.62-2.72 (m, 1H), 2.85-3.05 (m, 4H), 3.12-3.22 (m, 1H), 3.38 (dd, J=3Hz, 9Hz, 1H), 3.49-3.57 (m, 1H), 3.62 (d, J=9Hz, 1H), 3.82 (s, 3H), 5.96 (s, 2H),

6.73 (d, J=8Hz, 1H), 6.84 (dd, J=1Hz, 8Hz, 1H), 6.85 (d, J=9Hz, 2H), 7.02 (d, J=1Hz, 1H), 7.28 (d, J=9Hz, 2H), 7.39-7.54 (m, 3H), 7.70 (d, J=7Hz, 2H). MS (DCI/NH_3) m/e 567 $(M+H)^+$.

Example 121

trans,trans-1-(2-(N-(4-Methoxybenzenesulfonyl)-N-propylamino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 96-97 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (t, J=7Hz, 3H), 1.34 (sextet, J=7Hz, 2H), 2.20-2.30 (m, 1H), 2.62-2.71 (m, 1H), 2.82-3.03 (m, 4H), 3.08-3.18 (m, 2H), 3.38 (dd, J=3Hz, 9Hz, 1H), 3.48-3.56 (m, 1H), 3.62 (d, J=9Hz, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 5.95 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.81-6.89 (m, 5H), 7.01 (d, J=1Hz, 1H), 7.28 (d, J=8Hz, 2H), 7.62 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 597 $(M+H)^+$.

Example 122

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(2-methoxyethoxy-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

2-Hydroxy-5-methoxyacetophenone was treated with sodium hydride and bromoethyl methyl ether in THF at 70 °C to provide ethyl 2-methoxyethoxy-4-methoxybenzoylacetate which was treated by the procedures described in Example 1 to provide the title compound as a white solid. m.p. 63-65 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, J=7Hz, 3H), 0.89 (t, J=7Hz, 3H), 1.16 (sextet, J=7Hz, 2H), 1.28 (sextet, J=7Hz, 2H), 1.45-1.52 (m, 4H), 2.87-2.94 (m, 2H), 3.00-3.16 (m, 3H), 3.26-3.36 (m, 2H), 3.43 (s, 3H), 3.47-3.54 (m, 3H), 3.66-3.72 (m, 2H), 3.78 (s, 3H), 3.76-3.84 (m, 1H), 4.02-4.10 (m, 2H), 4.25 (d, J=9Hz, 1H), 5.92 (s, 2H), 6.40 (d, J=2Hz, 1H), 6.52 (dd, J=2Hz, 9Hz, 1H), 6.70 (d, J=8Hz, 1H), 6.83 (dd, J=1Hz, 8Hz, 1H), 5.98 (d, J=2Hz, 1H), 7.53 (d, J=9Hz, 1H). MS (DCI/NH_3) m/e 585 $(M+H)^+$.

Example 123

trans,trans-1-(2-(N-Propyl-N-(2,4-dimethylbenzenesulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 88-90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.69 (t, J=7Hz, 3H), 1.32 (sextet, J=7Hz, 2H), 2.12-2.20 (m, 1H), 2.32 (s, 3H), 2.47 (s, 3H), 2.62-2.69 (m, 1H), 2.78 (t, J=9Hz, 1H), 2.89 (dd, J=8Hz, 1H), 3.02 (sextet, J=9Hz, 2H), 3.15-3.32 (m, 3H), 3.46-3.55 (m, 1H), 3.60 (d, J=9Hz, 1H), 3.82 (s, 3H), 5.96 (s, 2H), 6.72 (d, J=7Hz, 1H), 6.80 (dd, J=1Hz, 9Hz,

1H), 6.86 (d, J=9Hz, 2H), 6.97 (d, J=1Hz, 1H), 7.03 (bs, 2H), 7.29 (d, J=9Hz, 1H). MS (DCI/NH_3) m/e 595 $(M+H)^+$.

Example 124

trans,trans-1-(2-(N-Propyl-N-(3-chloropropylsulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 75-76 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J=7Hz, 3H), 1.45 (sextet, J=7Hz, 2H), 2.15-2.31 (m, 3H), 2.70-2.80 (m, 1H), 2.85-3.10 (m, 6H), 3.23-3.31 (m, 2H), 3.43 (bd, J=9Hz, 1H), 3.55-3.66 (m, 4H), 3.81 (s, 3H), 5.94 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.82 (d, J=8Hz, 1H), 6.86 (d, J=8Hz, 2H), 7.00 (s, 1H), 7.33 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 567 $(M+H)^+$.

Example 125

trans,trans-1-(2-(N-Propyl-N-(2-methoxyethylsulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, *trans,trans*-1-(2-(N-Propyl-N-(vinylsulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid was prepared. Ester hydrolysis using aqueous sodium hydroxide in methanol afforded the title compound as a white solid. m.p. 62-64 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J=7Hz, 3H), 1.42 (sextet, J=7Hz, 2H), 2.23-2.32 (m, 1H), 2.72-2.79 (m, 1H), 2.86-3.05 (m, 4H), 3.10-3.27 (m, 4H), 3.32 (s, 3H), 3.43 (dd, J=3Hz, 9Hz, 1H), 3.53-3.58 (m, 1H), 3.65 (d, J=9Hz, 1H), 3.69 (t, J=6Hz, 2H), 3.80 (s, 3H), 5.94 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.82 (dd, J=1Hz, 8Hz, 1H), 6.87 (d, J=8Hz, 2H), 7.02 (d, J=1Hz, 1H), 7.33 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 549 $(M+H)^+$.

Example 126

trans,trans-1-(2-(N-Propyl-N-(2-ethoxyethylsulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 58-60 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J=7Hz, 3H), 1.18 (t, J=7Hz, 3H), 1.43 (sextet, J=7Hz, 2H), 2.24-2.33 (m, 1H), 2.70-2.80 (m, 1H), 2.87-3.05 (m, 4H), 3.13-3.20 (m, 2H), 3.22-3.32 (m, 2H), 3.42 (dd, J=2Hz, 9Hz, 1H), 3.46 (q, J=7Hz, 2H), 3.52-3.58 (m, 1H), 3.65 (d J=9Hz, 1H), 3.72 (t, J=6Hz, 2H), 3.80 (s, 3H), 5.95 (s, 2H), 6.73 (d, J=7Hz, 1H), 6.83 (dd, J=1Hz, 7Hz, 1H), 6.87 (d, J=8Hz, 2H), 7.00 (d, J=1Hz, 1H), 7.32 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 563 $(M+H)^+$.

Example 127

trans,trans-1-(2-(N-Propyl-N-(5-dimethylamino-1-naphthylsulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a yellow solid. m.p. 102-104 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.62 (t, J=7Hz, 3H), 1.28 (sextet, J=7Hz, 2H), 2.12-2.20 (m, 1H), 2.78 (t, J=9Hz, 1H), 2.88 (s, 6H), 2.72-2.89 (m, 1H), 3.05-3.12 (m, 2H), 3.26-3.45 (m, 3H), 3.45-3.52 (m, 1H), 3.58 (d, J=9Hz, 1H), 6.97 (d, J=1Hz, 1H), 7.13 (d, J=7Hz, 1H), 7.26 (d, J=8Hz, 1H), 7.42-7.50 (m, 2H), 8.08 (dd, J=1Hz, 7Hz, 1H), 8.20 (d, J=8Hz, 1H), 8.48 (d, J=8Hz, 1H). MS (DCI/NH_3) m/e 660 $(M+H)^+$.

Example 128

trans,trans-1-(2-(N-Propyl-N-(ethylsulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 70-72 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J=8Hz, 3H), 1.28 (t, J=7Hz, 3H), 1.43 (q, J=8Hz, 2H), 2.22-2.30 (m, 1H), 2.71-2.80 (m, 1H), 2.82-3.10 (m, 6H), 3.18-3.32 (m, 2H), 3.43 (dd, J=3Hz, 9Hz, 1H), 3.53-3.60 (m, 1H), 3.65 (d, J=9Hz, 1H), 3.80 (s, 3H), 5.96 (s, 2H), 6.73 (d, J=7Hz, 1H), 6.82 (dd, J=1Hz, 7Hz, 1H), 6.88 (d, J=8Hz, 2H), 7.00 (d, J=1Hz, 1H),. 7.32 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 519 $(M+H)^+$.

Example 129

trans,trans-1-(2-(N-Propyl-N-(4-methylbenzenesulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 78-79 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (t, J=7Hz, 3H), 1.33 (sextet, J=7Hz, 2H), 2.20-2.30 (m, 1H), 2.40 (s, 3H), 2.61-2.72 (m, 1H), 2.83-3.05 (m, 4H), 3.08-3.19 (m, 2H), 3.48 (dd, J=3Hz, 9Hz, 1H), 3.49-3.57 (m, 1H), 3.62 (d, J=9Hz, 1H), 3.81 (s, 3H), 5.95 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.82 (d, J=8Hz, 1H), 6.87 (d, J=8Hz, 2H), 7.00 (s, 1H), 7.21 (d, J=8Hz, 2H), 7.29 (d, J=8Hz, 2H), 7.57 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 581 $(M+H)^+$.

Example 130

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(3-pyridyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Methyl nicotinoyl acetate was prepared by the method of Wenkert, et al., J. Org. Chem. 48: 5006 (1983) and treated by the procedures described in Example 1 to provide the

title compound as a white solid. m.p. 167-168 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J-7Hz, 3H), 0.89 (t, J=7Hz, 3H), 1.14 (sextet, J=7Hz, 2H), 1.23-1.48 (m, 6H), 2.86-3.20 (m, 6H), 3.34-3.43 (m, 2H), 3.57 (dd, J=3Hz, 9Hz, 1H), 3.75-3.83 (m, 1H), 4.08 (d, J=9Hz, 1H), 5.93 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.90 (dd, J=2Hz, 8Hz, 1H), 7.03 (d, J=2Hz, 1H), 7.38 (dd, J=4Hz, 8Hz, 1H), 8.04 (d, J=8Hz, 1H), 8.48 (dd, J=2Hz, 4Hz, 2H). MS (DCI/NH_3) m/e 482 $(M+H)^+$.

Example 131

trans,trans-1-(2-(N-Propyl-N-(n-butylsulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 65-66 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J=7Hz, 3H), 0.92 (t, J=7Hz, 3H), 1.31-1.46 (m, 4H), 1.68 (quintet, J=7Hz, 2H), 2.21-2.32 (m, 1H), 2.70-3.08 (m, 7H), 3.12-3.23 (m, 2H), 3.42 (dd, J=2Hz, 9Hz, 1H), 3.52-3.58 (m, 1H), 3.64 (d, J=9Hz, 1H), 3.80 (s, 3H), 5.96 (s, 2H), 6.72 (d, J=7Hz, 1H), 6.83 (dd, J=1Hz, 7Hz, 1H), 6.86 (d, J=8Hz, 2H), 7.00 (d, J=1Hz, 1H), 7.32 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 547 $(M+H)^+$.

Example 132

trans,trans-1-(2-(N-Propyl-N-(4-chlorobenzenesulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 105-106 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.72 (t, J=7Hz, 3H), 1.34 (sextet, J=7Hzm 2H), 2.56-2.62 (m, 1H), 2.78-2.86 (m, 1H), 2.96-3.03 (m, 3H), 3.13-3.26 (m, 3H), 3.51 (dd, J=5Hz, 9Hz, 1H), 3.62-3.68 (m, 1H), 3.80 (s, 3H), 3.94 (d, J=9Hz, 1H), 5.92 (s, 2H), 6.75 (d, J=8Hz, 1H), 6.84 (dd, J=2Hz, 8Hz, 1H), 6.94 (d, J=8Hz, 2H), 6.98 (d, J=2Hz, 1H), 7.36 (d, J=8Hz, 1H), 7.49 (d, J=8Hz, 1H), 7.68 (d, J=8Hz, 1H). MS (DCI/NH_3) m/e 601 $(M+H)^+$.

Example 133

trans,trans-1-(2-(N-Propyl-N-(benzylsulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 88-89 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.72 (t, J=7Hz, 3H), 1.32 (sextet, J=7Hz, 2H), 2.06-2.16 (m, 1H), 2.56-2.67 (m, 1H), 2.75-3.10 (m, 6H), 3.30 (dd, J=2Hz, 9Hz, 1H), 5.95 (s, 2H), 6.73 (d, J=7Hz, 1H), 6.80 (dd, J=1Hz, 7Hz, 1H), 6.86 (d, J=8Hz, 2H), 6.97 (d, J=1Hz, 1H), 7.27-7.35 (m, 7H). MS (DCI/NH_3) m/e 581 $(M+H)^+$.

Example 134

trans,trans-1-(2-(N-Propyl-N-(4-fluorobenzenesulfonyl)amino)ethyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 91-93 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (t, J=7Hz, 3H), 1.44 (sextet, J=7Hz, 2H), 2.18-2.27 (m, 1H), 2.56-2.67 (m, 1H), 2.78-2.87 (m, 2H), 2.97 (septet, J=8Hz, 2H), 3.11-3.16 (m, 2H), 3.33 (dd, J=2Hz, 9Hz, 1H), 3.43-3.50 (m, 1H), 3.57 (d, J=9Hz, 1H), 3.78 (s, 3H), 7.08 (t, J=8Hz, 2H), 7.24 (d, J=8Hz, 2H), 7.69 (dd, J=5Hz, 8Hz, 2H). MS (DCI/NH_3) m/e 585 $(M+H)^+$.

Example 135

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(4-benzofuranyl)pyrrolidine-3-carboxylic acid

Example 135A

Benzofuran-4-carboxaldehyde

To a suspension of 60% sodium hydride in mineral oil (4.00 g, 100 mmol, 1.25 eq) in DMF (60 mL) at 0 °C was added a solution of 3-bromophenol (13.8 g, 80 mmol) in DMF (5 mL). After 10 minutes, bromoacetaldehyde diethyl acetal (14.9 mL, 96.6 mmol, 1.24 eq) was added, and the resultant mixture then heated at 120 °C for 2.5 hours. The mixture was cooled to room temperature and was poured into water, and extracted once with ether. The organic solution was dried over $MgSO_4$, filtered, evaporated and vacuum distilled to yield a colorless liquid (17.1 g, 74%). b.p. 160-163 °C at 0.4 mm Hg.

To warm polyphosphoric acid (15.3 g) was added a solution of the above compound (17.1 g, 59.3 mmol) in benzene (50 mL). The resultant mixture was heated under reflux with vigorous stirring for 4 hours, after which time the benzene layer was carefully decanted off, and the lower layer washed once with hexanes. The combined organic solutions were concentrated *in vacuo*, and then vacuum distilled to yield a colorless liquid (8.13 g, 70%). b.p. 62-72 °C at 0.6 mm Hg.

To a solution of the above compounds (8.11 g, 41.5 mmol) in ether (80 mL) at -78 °C was added 1.7 M t-butyllithium (48.8 mL, 83 mmol, 2 eq) such that the temperature did not exceed -70 °C. After stirring for 15 minutes, a solution of DMF (6.5 mL, 83 mmol, 2 eq) in ether (20 mL) was added, and the mixture allowed to warm to room temperaure over 2 hours. The mixture was poured into water and the phases separated. The organic solution was dried over $MgSO_4$ and concentated *in vacuo*. The residue was purified by flash chromatography on

silica gel eluting with 10% ether in hexanes to yield benzofuran-6-carboxaldehyde (1.22 g) and benzofuran-4-carboxaldehyde (1.86 g), both as colorless oils.

Example 135B

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(4-benzofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared using the procedures described in Examples 1 and 49 substituting the compound resulting from Example 135A in Example 49A for piperonal. ^{1}H NMR (300 MHz, $CDCl_3$) (minor rotamer) δ 7.59 (1H, t, J=3Hz), 7.4-7.2 (6H, m), 6.8 (2H, d, J=8Hz), 4.03 (1H, m), 3.94 (1H, dd, J=8Hz, 3Hz), 3.77 (3H, s), 3.61 (1H, dd, J=8Hz, 7 3Hz), 3.42 (1H, dd, J=11Hz, 5Hz), 3.40-2.90 (5H, m), 2.82 (2.81) (3H, s), 1.50 (2H, septet, J=7Hz), 0.82 (0.75) (3H, t, J=7Hz). MS (DCI/NH_3) m/e 451 $(M+H)^+$. Anal.calc. for $C_{26}H_{30}N_2O_5 \cdot$ AcOH: C, 65.87; H, 6.71; N ,5.49. Found: C, 66.04; H, 6.42; N, 5.60. s

Example 136

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(6-benzofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared using the procedures described in Examples 1 and 49 substituting benzofuran-6-carboxaldehyde, prepared as described in Example 135A, in Example 49A for piperonal. ^{1}H NMR (300 MHz, $CDCl_3$) (minor rotamer) δ 7.65 (1H, bd), 7.60 (1H, d, J=2Hz), 7.55 (1H, d, J=8Hz), 7.35 (3H, m), 6.85 (2H, dd, J=8Hz, 3Hz), 6.75 (1H, dd, J=3Hz, 2Hz), 3.83 (2H, m), 3.79 (3H, s), 3.60-3.0 (7H, m), 2.91 (2.83) (s, 3H), 1.51 (2H, septet, J=7Hz), 0.83 (0.78) (3H, t, J=7Hz). MS (DCI/NH_3) m/e 451 $(M+H)^+$. Anal.calc. for $C_{26}H_{30}N_2O_5 \cdot 0.5\ H_2O$: C, 67.96; H, 6.80; N, 6.10. Found: C, 67.90; H, 6.71; N, 6.07.

Example 137

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(6-benzo-2,3-dihydrofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by catalytic hydrogenation (4 atmospheres of H_2 in AcOH, followed by preparative hplc) of the compound resulting from Example 136 ^{1}H NMR (300 MHz, $CDCl_3$) (minor rotamer) δ 7.49 (7.47) (2H, d, J=8Hz), 7.19 (1H, d, J=8Hz), 7.00 (1H, m), 7.82 (3H, m), 5.40 (1H, dd, J=11Hz, 7Hz), 4.58 (2H, t, J=8Hz), 4.18 (1H, m), 4.10 (1H, m), 3.88 (1H, m), 3.79 (3H, s), 3.60 (1H, m), 3.35 (1H, m), 3.19 (2H, t, J=8Hz), 3.00 (4H, m), 2.91 (2.78) (s, 3H), 1.53 (1.40) (2H, septet, J=7Hz), 0.88 (0.78) (3H, t, J=7Hz). MS (DCI/NH_3) m/e 453 $(M+H)^+$. Anal.calc. for $C_{26}H_{32}N_2O_5 \cdot 1.25$ TFA: C, 57.53; H, 5.63; N, 4.71. Found: C, 57.68; H, 5.68; N, 4.70.

Example 138

<u>*trans,trans*-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(4-benzofuranyl)pyrrolidine-3-carboxylic acid</u>

The title compound was prepared by the procedures described in Examples 1 and 49 substituting benzofuran-4-carboxaldehyde in Example 49A for piperonal and substituting N,N-dibutyl bromoacetamide for N-methyl-N-propyl bromoacetamide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (1H, d, J=3Hz), 7.39 (1H, dt, J=8Hz, 2Hz), 7.34 (3H, m), 7.26 (1H, d, J=2Hz), 7.23 (1H, d, J=8Hz), 6.84 (2H, d, J=8Hz), 4.02 (1H, ddd, J=8, 6Hz,4Hz), 3.89 (1H, d, J=9Hz) 3.79 (3H, s), 3.67 (1H, dd, J=10Hz, 3Hz), 3.44 (2H, m), 3.35-3.15 (3H, m), 3.00 (2H, m), 2.84 (1H, d, J=14Hz), 1.43 (3H, m), 1.23 (3H, m), 1.08 (2H, m), 0.87 (3H, t, J=7Hz), 0.82 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 507 $(M+H)^+$. Anal.calc. for $C_{30}H_{38}N_2O_5$: C, 71.12; H, 7.56; N, 5.53. Found: C, 70.86; H, 7.45; N, 5.24.

Example 139

<u>*trans,trans*-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(4-benzofuranyl)pyrrolidine-3-carboxylic acid</u>

The title compound was prepared by the procedures described in Examples 1 and 49 substituting benzofuran-5-carboxaldehyde, prepared by the procedures described in Example 135A substituted 4-bromophenol for 3-bromophenol, in Example 49A for piperonal and substituting N,N-dibutyl bromoacetamide for N-methyl-N-propyl bromoacetamide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (1H, bd), 7.59 (1H, d, J=2Hz), 7.43 (2H, m), 7.33 (2H, d, J=8Hz), 6.85 (2H, d, J=8Hz), 6.73 (1H, dd, J=3Hz, 1Hz), 3.82 (1H, d, J=11Hz), 3.89 (1H, d, J=9Hz) 3.79 (3H, s), 3.53 (1H, dd, J=10Hz, 3Hz), 3.44 (2H, m), 3.30 (1H, m), 3.20-2.95 (5H, m), 2.82 (1H, d, J=14Hz), 1.43 (3H, m), 1.23 (3H, m), 1.08 (2H, m), 0.87 (3H, t, J=7Hz), 0.82 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 507 $(M+H)^+$. Anal.calc. for $C_{30}H_{38}N_2O_5$: C, 71.12; H, 7.56; N, 5.53. Found: C, 70.73; H, 7.45; N, 5.29.

Example 140

<u>*trans,trans*-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(6-benzofuranyl)pyrrolidine-3-carboxylic acid</u>

The title compound was prepared by the procedures described in Examples 1 and 49 substituting benzofuran-6-carboxaldehyde in Example 49A for piperonal and substituting N,N-dibutyl bromoacetamide for N-methyl-N-propyl bromoacetamide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, bd), 7.59 (1H, d, J=2Hz), 7.53 (1H, d, J=8Hz), 7.36 (3H, m), 6.85 (2H, d, J=8Hz), 6.73 (1H, dd, J=3Hz, 1Hz), 3.82 (1H, d, J=11Hz), 3.89 (1H, d, J=9Hz) 3.79 (3H,

s), 3.53 (1H, dd, J=10Hz, 3Hz), 3.44 (2H, m), 3.30 (1H, m), 3.20-2.95 (5H, m), 2.80 (1H, d, J=14Hz), 1.43 (3H, m), 1.23 (3H, m), 1.08 (2H, m), 0.87 (3H, t, J=7Hz), 0.82 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 507 $(M+H)^+$. Anal.calc. for $C_{30}H_{38}N_2O_5 \cdot 0.75\ H_2O$: C, 69.28; H, 7.65; N, 5.39. Found: C, 69.11; H, 7.33; N, 5.32.

Example 141

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(6-benzo-2,3-dihydrofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by catalytic hydrogenation of the compound resulting from Example 140 (4 atmospheres of H_2 in AcOH, followed by preparative hplc). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (2H, d, J=8Hz), 7.16 (1H, d, J=8Hz), 6.97 (1H, dd, J=8Hz, 2Hz), 6.89 (3H, m), 5.90 (1H, bs) 4.57 (2H, t, J=9Hz), 4.93 (2H, m), 3.80 (3H, s), 3.70-3.58 (2H, m), 3.40 (1H, m), 3.30-2.90 (8H, m), 1.40 (2H, m), 1.29 (3H, m), 1.08 (2H, m), 0.92 (3H, t, J=7Hz), 0.82 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 509 $(M+H)^+$. Anal.calc. for $C_{30}H_{40}N_2O_5 \cdot 0.85$ TFA: C, 62.88; H, 6.80; N, 4.63. Found: C, 63.04; H, 6.66; N, 4.60.

Example 142

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(5-indanyl)pyrrolidine-3-carboxylic acid

Example 142A

Indane-5-carboxaldehyde

Indane-5-carboxaldehyde was prepared by formylation of indane under the conditions described for 2,3-dihydrobenzofuran in Example 52A. The resultant mixture of 4- and 5-carboxaldehydes was purified as follows: to a 6:1 mixture of indane-4-carboxaldehyde and indane-5-carboxaldehyde (3.46 g, 23 mmol) was added aniline (2.20 g, 23 mmol, 1 eq). The resultant solution slowly solidfied to a mixture of imines which was recrystallized from hot acetonitrile to yield the 5-aldimine as a white solid. The aldimine (2.65 g) was suspended in water (6 mL), and treated with 4 N hydrochloric dioxane (10 mL). The mixture was boiled for 1 hour, cooled to room temperature, and poured into ether. The organic solution was dried over $MgSO_4$, filtered, and concentated *in vacuo*. Vacuum distillation of the residue afforded indane-5-carboxaldehyde (1.54 g, 88%) as a colorless liquid. b.p. 88-90 °C at 0.9 mm Hg.

Example 142B

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(5-indanyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting indane-5-carboxaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) (minor rotamer) δ 7.25-7.1 (5H, m), 6.78 (2H, d, J=8Hz), 3.89 (1H, d, J=8Hz), 3.75 (3H, s), 3.50-2.90 (6H, m), 2.88 (6H, t, J=6Hz), 2.82 (2.80) (3H, s), 2.04 (2H, t, J=8Hz), 1.48 (2H, septet, J=7Hz), 0.83 (0.73) (3H, t, J=7Hz). MS (DCI/NH_3) m/e 451 $(M+H)^+$, 473 $(M+Na)^+$. Anal.calc. for $C_{27}H_{34}N_2O_4 \cdot 2.5\ H_2O$: C, 65.44; H, 7.93; N, 5.65. Found: C, 65.36; H, 7.45; N, 5.53.

Example 143

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(6-indolyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting indole-6-carboxaldehyde, prepared by the method of Rapoport, J. Org. Chem. 51: 5106 (1986), for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) (minor rotamer) δ 8.43 (1H, brs), 7.57 (1H, d, J=8Hz), 7.43 (1H, s), 7.31 (2H, dd, J=6Hz, 3Hz), 7.22 (1H, d, J=8Hz), 7.1 (1H, t, J=3Hz), 6.78 (2H,dd, J=6Hz, 3Hz), 6.45 (1H, m), 3.93 (1H, dd, J=6Hz, 3Hz), 3.80 (1H, m), 3.73 (3H, s), 3.60-2.90 (6H, m), 2.86 (2.82) (3H, s), 1.47 (2H, septet, J=7Hz), 0.83 (0.73) (3H, t, J=7Hz). MS (DCI/NH_3) m/e 450 $(M+H)^+$. Anal.calc. for $C_{26}H_{31}N_3O_4 \cdot 0.75\ H_2O$: C, 67.44; H, 7.07; N, 9.07. Found: C, 67.42; H, 7.09; N, 8.91.

Example 144

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(3,4-difluorophenyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 3,4-difluorobenzaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) (minor rotamer) δ 7.60-7.3 (4H, m), 7.13 (1H, q, J=9Hz), 6.90 (2H, d, J=8Hz), 3.90 (1H, m), 3.79 (3H, s), 3.60-2.95 (6H, m), 2.92 (2.78) (3H, s), 1.55 (2H, septet, J=7Hz), 0.88 (0.73) (3H, t, J=7Hz). MS (DCI/NH_3) m/e 447 $(M+H)^+$. Anal.calc. for $C_{24}H_{28}F_2N_2O_4 \cdot 1.80\ H_2O$: C, 60.19; H, 6.65; N, 5.85. Found: C, 60.13; H, 6.34; N, 5.84.

Example 145

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(phenyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting benzaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) (minor rotamer) δ 7.53 (4H, d, J=6Hz), 7.40-7.20 (3H, m), 6.88 (2H, d, J=8Hz), 3.90 (1H, m),

3.79 (3H, s), 3.70-2.95 (8H, m), 2.90 (2.79) (3H, s), 1.50 (2H, sept, J=7Hz), 0.87 (0.72) (3H, t, J=7Hz). MS (DCI/NH_3) m/e 411 $(M+H)^+$. Anal.calc. for $C_{24}H_{30}N_2O_4 \cdot 2.00\ H_2O$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.37; H, 7.43; N, 6.29.

Example 146

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(4-hydroxyphenyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 4-hydroxybenzaldehyde for piperonal in Example 49A. ^1H NMR (300 MHz, $CDCl_3$-CD_3OD) (minor rotamer) δ 7.35 (2H, d, J=8Hz), 7.28 (2H, dd, J=7Hz, 3Hz), 6.90 (2H, dd, J=7Hz, 3Hz), 6.89 (2H, d, J=8Hz), 3.81 (3H, s), 3.65 (1H, d, J=8Hz), 3.70-3.00 (8H, m), 2.92 (2.83) (3H, s), 1.50 (2H, septet, J=7Hz), 0.87 (0.77) (3H, t, J=7Hz). MS (DCI/NH_3) m/e 427 $(M+H)^+$. Anal.calc. for $C_{24}H_{30}N_2O_5 \cdot 1.00\ H_2O$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.82; H, 7.39; N, 6.46.

Example 147

trans,trans-1-(N-Methyl-N-propylaminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(2,4-dimethoxyphenyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 2,4-dimethoxybenzaldehyde for piperonal in Example 49A. ^1H NMR (300 MHz, $CDCl_3$-CD_3OD) (minor rotamer) δ 7.61 (1H, d, J=8Hz), 7.30 (2H, d, J=8Hz), 6.82 (2H, d, J=8Hz), 6.55 (1H, d, J=8Hz), 6.45 (1H, d, J=3Hz), 3.90 (1H, m), 3.81 (3H, s), 3.79 (3H, s), 3.77 (3H, s), 3.70-2.90 (8H, m), 2.85 (3H, s), 1.50 (2H, sept, J=7Hz), 0.87 (0.77) (3H, t, J=7Hz). MS (DCI/NH_3) m/e 471 $(M+H)^+$. Anal.calc. for $C_{26}H_{34}N_2O_6 \cdot 0.75\ H_2O$: C, 64.51; H, 7.39; N, 5.79. Found: C, 64.65; H, 7.07; N, 5.75.

Example 148

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(5-benzo-2,3-dihydrofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 2,3-dihydrobenzofuran-5-carboxaldehyde for piperonal in Example 49A. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (2H, d, J=8Hz), 7.27 (1H, d, J=2Hz), 7.18 (1H, dd, J=7Hz, 3Hz), 6.86 (2H, d, J=8Hz), 6.72 (1H, d, J=8Hz), 4.56 (2H, t, J=7Hz), 3.78 (3H, s), 3.62 (1H, m), 3.50-3.25 (4H, m), 3.17 (2H, t, J=7Hz), 3.15-2.90 (5H, m), 2.79 (1H, d, J=14Hz), 1.43 (3H, m), 1.26 (3H, m), 1.08 (2H, m), 0.87 (3H, t, J=7Hz), 0.81 (3H, t, J=7Hz). MS

(DCI/NH_3) m/e 509 $(M+H)^+$. Anal.calc. for $C_{30}H_{40}N_2O_5 \cdot 0.25\ H_2O$: C, 70.22; H, 7.95; N, 5.46. Found: C, 70.21; H, 7.92; N, 5.36.

Example 149

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 4-methoxybenzaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (2H, d, J=8Hz), 7.30 (2H, d, J=8Hz), 6.87 (4H, dd, J=7Hz, 3Hz), 3.78 (3H, s), 3.76 (3H, s), 3.63 (1H, m), 3.50-3.20 (4H, m), 3.15-2.90 (5H, m), 2.78 (1H, d, J=14Hz), 1.43 (3H, m), 1.27 (3H, m), 1.09 (2H, m), 0.87 (3H, t, J=7Hz), 0.81 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 497 $(M+H)^+$. Anal.calc. for $C_{29}H_{40}N_2O_5$: C, 70.13; H, 8.12; N, 5.64. Found: C, 69.78; H, 8.10; N, 5.54.

Example 150

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(3,4-difluorophenyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 3,4-difluorobenzaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (1H, m), 7.30 (2H, d, J=8Hz), 7.20-7.00 (2H, m), 6.87 (2H, d, J=8Hz), 3.78 (3H, s), 3.79 (1H, m), 3.62 (1H, m), 3.50-3.30 (3H, m), 3.23 (1H, m), 3.15-2.90 (4H, m), 2.78 (1H, d, J=14Hz), 1.43 (2H, m), 1.27 (4H, m), 1.08 (2H, m), 0.85 (3H, t, J=7Hz), 0.80 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 503 $(M+H)^+$. Anal.calc. for $C_{28}H_{36}F_2N_2O_4 \cdot 1\ H_2O$: C, 64.60; H, 7.36; N, 5.38. Found: C, 64.59; H, 7.20; N, 5.35.

Example 151

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(2,4-dimethoxyphenyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 2,4-dimethoxybenzaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (2H, d, J=8Hz), 7.20 (1H, d, J=8Hz), 6.92 (2H, d, J=8Hz), 6.60 (1H, d, J=3Hz), 6.49 (1H, dd, J=6Hz, 2Hz), 5.35 (1H, d, J=8Hz), 4.20 (3H, m), 4.10 (3H, s), 3.83 (3H, s), 3.81 (3H, s), 3.75 (3H, m), 3.17 (2H, hep, J=7Hz), 3.05 (2H, t, J=7Hz), 1.30 (4H, m), 1.07 (4H, m), 0.87 (3H, t, J=7Hz), 0.80 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 527 $(M+H)^+$. Anal.calc. for $C_{30}H_{42}N_2O_6 \cdot 1.30$ TFA: C, 58.02; H, 6.47; N, 4.15. Found: C, 57.92; H, 6.43; N, 4.07.

Example 152

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-phenyl-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting ethyl benzoylacetate in Example 49B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.25 (5H, m), 7.04 (1H, d, J=3Hz), 6.87 (1H, dd, J=7Hz, 3Hz), 6.74 (1H, d, J=8Hz), 5.94 (1H, d, J=4Hz), 5.92 (1H, d, J=4Hz), 3.85 (1H, d, J=8Hz), 3.64 (1H, m), 3.42 (3H, m), 3.27 (2H, m), 3.20-2.90 (5H, m), 2.81 (1H, d, J=14Hz), 1.43 (2H, m), 1.27 (4H, m), 1.05 (2H, m), 0.85 (3H, t, J=7Hz), 0.80 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 481 $(M+H)^+$. Anal.calc. for $C_{28}H_{36}N_2O_5$: C, 69.98; H, 7.55; N, 5.83. Found: C, 69.69; H, 7.63; N, 5.71.

Example 153

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-phenyl-4-(5-benzo-2,3-dihydrofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting ethyl benzoylacetate in Example 49B and 2,3-dihydrobenzofuran-5-carboxaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (2H, m), 7.40 (4H, m), 7.13 (1H, dd, J=7Hz, 3Hz), 6.72 (1H, d, J=8Hz), 5.40 (1H, d, J=10Hz), 4.56 (2H, t, J=8Hz), 4.18 (1H, d, J=14Hz), 4.07 (2H, m), 3.79 (2H, m), 3.48 (1H, d, J=14Hz), 3.35 (1H, m), 3.28 (3H, m), 2.95 (2H, m), 1.47 (2H, m), 1.28 (4H, m), 1.10 (2H, m), 0.93 (3H, t, J=7Hz), 0.78 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 479 $(M+H)^+$. Anal.calc. for $C_{29}H_{38}N_2O_4 \cdot 1.10$ TFA: C, 62.04; H, 6.52; N, 4.64. Found: C, 61.89; H, 6.44; N, 4.57.

Example 154

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-t-butylphenyl)-4-(5-benzo-2,3-dihydrofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting t-butyl benzoylacetate, prepared by the method of Krapcho et al., Org. Syn. 47:20 (1967) starting from 4-t-butylacetophenone, in Example 49B and 2,3-dihydrobenzofuran-5-carboxaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.30 (6H, m), 6.90 (1H, m), 4.50 (2H, m), 3.95 (1H, m), 3.85-2.95 (11H, m), 2.90 (1H, d, J=14Hz), 1..58 (2H, m), 1.50 (7H, m), 1.41 (6H, s), 1.10 (2H, m), 1.00 (3H, t, J=7Hz), 0.90 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 535 $(M+H)^+$. Anal.calc. for $C_{33}H_{46}N_2O_4 \cdot 0.25\ H_2O$: C, 73.50; H, 8.69; N, 5.19. Found: C, 73.57; H, 8.58; N, 5.14.

Example 155

trans,trans-2-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(4-fluorophenyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 4-fluorobenzaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, m), 7.42 (1H, dd, J=7Hz, 3Hz), 7.36 (2H, d, J=8Hz), 7.01 (3H, t, J=8Hz), 6.87 (1H, d, J=8Hz), 3.83 (1H, m), 3.8 (3H, s), 3.67 (1H, m), 3.47 (3H, m), 3.30-2.90 (5H, m), 2.82 (1H, d, J=14Hz), 1.43 (2H, m), 1.28 (4H, m), 1.08 (2H, m), 0.90 (3H, t, J=7Hz), 0.82 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 485 $(M+H)^+$. Anal.calc. for $C_{28}H_{37}FN_2O_4$: C, 69.40; H, 7.70; N, 5.78. Found: C, 69.03; H, 8.00; N, 5.74.

Example 156

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(3-furyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting β-oxo-3-furanpropionate in Example 49B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (2H, m), 6.97 (1H, d, J=3Hz), 6.85 (1H, dd, J=7Hz, 3Hz), 6.72 (1H, d, J=8Hz), 6.42 (1H, s), 5.94 (1H, d, J=4Hz), 5.92 (1H, d, J=4Hz), 3.90 (1H, m), 3.70-3.25 (5H, m), 3.20-2.90 (4H, m), 2.85 (1H, d, J=14Hz), 1.43 (2H, m), 1.40-1.05 (6H, m), 0.90 (6H, m). MS (DCI/NH_3) m/e 471 $(M+H)^+$. Anal.calc. for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.09; H, 7.24; N, 5.87.

Example 157

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(isopropyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting ethyl isobutyrylacetate in Example 49B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (1H, d, J=2Hz), 6.76 (1H, dd, J=6Hz, 2Hz), 6.71 (1H, d, J=8Hz), 5.92 (2H, s), 3.75 (1H, d, J=14Hz), 3.66 (1H, q, J=7Hz), 3.42 (3H, m), 3.25 (3H, m), 3.11 (2H,m), 2.83 (1H, t, J=7Hz), 1.88 (1H, m), 1.55 (4H, m), 1.32 (4H, m), 0.92 (12H, m). MS (DCI/NH_3) m/e 447 $(M+H)^+$. Anal.calc. for $C_{25}H_{38}N_2O_5 \cdot 0.50\ H_2O$: C, 65.91; H, 8.63; N, 6.15. Found: C, 66.07; H, 8.10; N, 6.03.

Example 158

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-t-butylphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting ethyl 4-t-butylbenzoylacetate, prepared by the method of Krapcho et al., Org. Syn. 47: 20 (1967) starting with 4-t-butylacetophenone), in Example 49B. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (4H, d, J=3Hz), 7.04 (1H, d, J=2Hz), 6.87 (1H, dd, J=8Hz, 3Hz), 6.74 (1H, d, J=9Hz), 5.94 (1H, d, J=4Hz), 5.92 (1H, d, J=4Hz), 3.77 (1H, d, J=14Hz), 3.65-3.25 (5H, m), 3.15-2.85 (4H, m), 2.73 (1H, d, J=14Hz), 1.45 (2H, m), 1.29 (13H, s), 1.00 (2H, m), 0.86 (3H, t, J=7Hz), 0.76 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 537 $(M+H)^+$. Anal.calc. for $C_{32}H_{44}N_2O_5$: C, 71.61; H, 8.26; N, 5.22. Found: C, 71.43; H, 8.09; N, 5.11.

Example 159

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-t-butylphenyl)-4-(5-benzo-2,3-dihydrofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting ethyl isobutyrylacetate in Example 49B and 2,3-dihydrobenzofuran-5-carboxaldehyde for piperonal in Example 49A. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (1H, s), 7.13 (1H, dd, J=7Hz, 2Hz), 6.82 (1H, d, J=8Hz), 4.68 (2H, t, J=8Hz), 4.48 (1H, s), 3.19 (3H, m), 3.80 (3H, m), 3.48 (2H, m), 3.3 (5H, m), 2.41 (1H, m), 1.65 (4H, m), 1.44 (4H, m), 1.21 (3H, d, J=5Hz), 1.17 (3H, d, J=5Hz), 1.05 (6H, m). MS (DCI/NH_3) m/e 445 $(M+H)^+$. Anal.calc. for $C_{26}H_{40}N_2O_4 \cdot 1.2$ TFA: C, 58.67; H, 7.14; N, 4.8.2 Found: C, 58.54; H, 7.25; N, 4.74.

Example 160

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(anti-4-methoxycyclohexyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

Example 160A

syn and anti Ethyl 4-methoxycyclohexanoylacetate

Syn, anti-4-Methoxycyclohexane carboxylic acid (5.00 g, 31.6 mmol) and carbonyldiimidazole (6.15 g, 37.9 mmol, 1.2 eq) were stirred in anhydrous tetrahydrofuran (50 mL) for 6 hours at room temperature. At the same time, magnesium chloride (3.01 g, 31.6 mmol) and ethyl malonate potassium salt (7.52 g, 44.2 mmol, 1.4 equivalents) were stirred in anhydrous tetrahydrofuran (75 mL) for 6 hours at 50 °C. The mixture was cooled to room temperature, and the imidazole-acid mixture added to it. The reaction stirred overnight at room temerature. The solvents were removed under reduced pressure, and the residue was taken up in chloroform/water. The organic phase washed with 5% potassium bisulfate, water, and brine, dried with magnesium sulfate, filtered, and concentrated under reduced pressure.

The residue was purified by flash chromatography on 175 g silica gel, eluting with 20% ethyl acetate in hexanes. Pure fractions of the syn and anti methoxycyclohexyl β-keto esters were obtained. The solvents were removed under reduced pressure to yield the trans-4-methoxycyclohexyl β-keto ester (914 mg) as a colorless oil and the cis 4-methoxycyclohexyl β keto ester (1.07 g) as a colorless oil.

Example 160B

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(anti-4-methoxycyclohexyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting the anti-compound resulting from Example 160A in Example 49B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (1H, d, J=2Hz), 6.76 (1H, dd, J=7Hz, 2Hz), 6.61 (1H, d, J=8Hz), 5.92 (2H, s), 3.69 (2H, m), 3.50-3.27 (5H, m), 3.26 (3H, s), 3.25-3.00 (3H, m), 2.88 (1H, m), 1.95 (2H, m), 1.62 (7H, m), 1.33 (9H, m), 0.97 (3H, t, J=7Hz), 0.92 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 517 $(M+H)^+$. Anal.calc. for $C_{29}H_{44}N_2O_6 \cdot 0.50\ H_2O$: C, 66.26; H, 8.63; N, 5.33. Found: C, 66.27; H, 8.50; N, 5.13.

Example 161

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(syn-4-methoxycyclohexyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting the syn-compound resulting from Example 160A in Example 49B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (1H, d, J=2Hz), 6.77 (1H, dd, J=6Hz, 2Hz), 6.61 (1H, d, J=8Hz), 5.92 (2H, s), 3.65 (2H, m), 3.42 (2H, m), 3.32 (3H, s), 3.30-3.00 (6H, m), 2.82 (1H, m), 2.10 (2H, m), 1.83 (2H, m), 1.52 (6H, m), 1.33 (4H, m), 1.20-1.00 (4H, m), 0.96 (3H, t, J=7Hz), 0.91 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 517 $(M+H)^+$. Anal.calc. for $C_{29}H_{44}N_2O_6 \cdot 0.30\ H_2O$: C, 66.72; H, 8.61; N, 5.37. Found: C, 66.76; H, 8.65; N, 5.28.

Example 162

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2,4-di(5-benzo-2,3-dihydrofuranyl)pyrrolidine-3-carboxylic acid

Example 162A

5-Acetyl-2,3-dihydrobenzofuran

To a 0 °C solution of acetyl chloride (1.64 mL, 23.0 mmol, 1.3 equivalents) in methylene chloride (30 mL) was added stannic chloride (2.49 mL, 21.3 mmol, 1.2 equivalents), maintaining the temperature below 5 °C. The solution was stirred 15 minutes at 0 °C, and then a solution of 2,3-dihydrofuran (2.00 mL, 17.7 mmol) in methylene chloride (5 mL) was added dropwise while maintaining the temperature below 8 °C. The dark red solution was stirred 1 hour at 2 °C and then poured into 50 mL of ice water. The reaction was stirred an additional 30 minutes, and the layers were separated. The organic layer was washed with water and aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on 150 g silica gel, eluting with 18% ethyl acetate in hexanes. The solvents were removed under reduced pressure to yield the title compound (2.68 g, 93%) as a yellow solid.

Example 162B

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2,4-di(5-benzo-2,3-dihydrofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting the compound resulting from Example 162A in Example 49B and 2,3-dihydrobenzofuran-5-carboxaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, s), 7.38 (1H, s), 7.06 (2H, m), 6.75 (1H, d, J=6Hz), 6.70 (1H, d, J=6Hz), 5.40 (1H, d, J=9Hz), 4.58 (4H, q, J=7Hz), 4.16 (1H, d, J=14Hz), 4.09 (2H, m), 3.82 (2H, m), 3.57 (1H, d, J=14Hz), 3.38 (1H, m), 3.30-3.05 (6H, m), 2.95 (2H, q, J=6Hz), 1.50 (2H, m), 1.30 (4H, m), 1.15 (2H, m), 0.94 (3H, t, J=7Hz), 0.83 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 521 $(M+H)^+$. Anal.calc. for $C_{31}H_{40}N_2O_5 \cdot 1.25$ TFA: C, 60.67; H, 6.27; N, 4.22. Found: C, 60.49; H, 6.18; N, 4.13.

Example 163

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(3-furyl)-4-(5-benzo-2,3-dihydrofuranyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting ethyl β-oxo-3-furanpropionate in Example 49B and 2,3-dihydrobenzofuran-5-carboxaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, m), 7.38 (1H, m), 7.13 (1H, s), 7.16 (1H, dd, J=7Hz, 3Hz), 6.70 (1H, d, J=8Hz), 6.41 (1H, m), 4.57 (2H, t, J=7Hz), 3.95 (1H, d, J=8Hz), 3.63 (1H, m), 3.55 (1H, d, J=14), 3.50-3.25 (4H, m), 3.18 (2H, t, J=6Hz), 3.15-2.95 (3H, m), 2.87 (1H, d, J=14Hz), 1.45 (4H, m), 1.35-1.10 (4H, m), 0.85 (6H, m). MS (DCI/NH_3) m/e 469 $(M+H)^+$. Anal.calc. for $C_{27}H_{36}N_2O_5 \cdot 0.25$ H_2O: C, 68.55; H, 7.78; N, 5.92. Found: C, 68.62; H, 7.68; N, 5.82.

Example 164

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(3-fluorophenyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 3-fluorobenzenecarboxaldehyde for piperonal in Example 49A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (2H, d, J=8Hz), 7.22 (2H, m), 6.91 (1H, m), 6.86 (2H, d, J=8Hz), 3.79 (1H, m), 3.78 (3H, s), 3.68 (1H, m), 3.55-3.37 (3H, m), 3.29 (1H, m), 3.15-2.90 (5H, m), 2.78 (1H, d, J=14Hz), 1.43 (2H, m), 1.25 (4H, m), 1.07 (2H, m), 0.87 (3H, t, J=7Hz), 0.80 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 485 $(M+H)^+$. Anal.calc. for $C_{28}H_{37}FN_2O_4 \cdot 0.25\ H_2O$: C, 68.76; H, 7.73; N, 5.73. Found: C, 68.87; H, 7.69; N, 5.67.

Example 165

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(4-methoxyphenyl)-4-(3-pyridyl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting 3-pyridinecarboxaldehyde for piperonal in Example 49A. The nitro styrene was prepared by the method of Bourguignon ,et al., Can. J. Chem. 63: 2354 (1985). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, bs), 8.73 (1H, bd, J=9Hz), 8.62 (1H, bd, J=7Hz), 7.78 (1H, bdd, J=9Hz, 3Hz), 7.38 (2H, d, J=10Hz), 6.90 (2H, d, J=10Hz), 4.39 (1H, d, J=12Hz), 3.95 (1H, m), 3.80 (3H, s), 3.79 (1H, m), 3.68 (1H, d, J=18Hz), 3.50-3.30 (3H, m), 3.25-2.90 (6H, m), 1.47 (2H, m), 1.31 (4H, m), 1.20 (2H, m), 0.92 (3H, t, J=7Hz), 0.83 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 468 $(M+H)^+$. Anal.calc. for $C_{27}H_{37}N_3O_4 \cdot 1.65$ TFA: C, 55.50; H, 5.94; N, 6.41. Found: C, 55.53; H, 5.90; N, 6.27.

Example 166

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(2-fluorophenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting ethyl 2-fluorobenzoylacetate in Example 49B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, dt, J=7Hz, 3Hz), 7.25 (1H, m), 7.13 (1H, dt, J=7Hz, 3Hz), 7.02 (2H, m), 6.88 (1H, dd, J=7Hz, 3Hz), 6.73 (1H, d, J=8Hz), 5.93 (1H, d, J=4Hz), 5.92 (1H, d, J=4Hz), 4.25 (1H, d, J=9Hz), 3.68 (1H, m), 3.42 (3H, m), 3.39 (1H, m), 3.20-2.95 (4H, m), 2.91 (1H, d, J=14Hz), 1.45 (3H, m), 1.26 (3H, m), 1.08 (2H, m), 0.87 (3H, t, J=7Hz), 0.81 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 499 $(M+H)^+$. Anal.calc. for $C_{28}H_{35}FN_2O_5 \cdot 0.25\ H_2O$: C, 66.85; H, 7.11; N, 5.57. Found: C, 66.51; H, 6.67; N, 5.18.

Example 167

trans,trans-1-(N,N-Di(n-butyl)aminocarbonylmethyl)-2-(3-fluorophenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

The title compound was prepared by the procedures described in Examples 1 and 49 substituting ethyl 3-fluorobenzoylacetate in Example 49B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, m), 7.18 (1H, d, J=7Hz), 7.15 (1H, m), 7.00 (1H, d, J=2Hz), 6.95 (1H, m), 6.86 (1H, dd, J=7Hz, 2Hz), 6.75 (1H, d, J=8Hz), 5.93 (1H, d, J=4Hz), 5.92 (1H, d, J=4Hz), 3.94 (1H, d, J=14Hz), 3.63 (1H, m), 3.42 (3H, m), 3.35-2.95 (5H, m), 2.87 (1H, d, J=14Hz), 1.44 (3H, m), 1.27 (3H, m), 1.10 (2H, m), 0.88 (3H, t, J=7Hz), 0.81 (3H, t, J=7Hz). MS (DCI/NH_3) m/e 499 $(M+H)^+$. Anal.calc. for $C_{28}H_{35}FN_2O_5$: C, 67.45; H, 7.08; N, 5.62. Found: C, 67.32; H, 7.05; N, 5.40.

Example 168

trans,trans-1-(4-N,N-Di(n-butyl)aminophenyl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

4-Nitro-1-fluorobenzene, ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate (the compound resulting from Example 6A), and diisopropylethylamine are heated in dioxane to give ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(4-nitrophenyl)-pyrrolidine-3-carboxylate. The nitro compound is hydrogenated to give the corresponding aminophenyl compound. The aminophenyl compound is reacted with butyraldehyde and sodium cyanoborohydride according to the method of Borch, J. Am Chem. Soc. 93: 2897 (1971) to give the corresponding N,N-dibutylaminophenyl compound. Hydrolysis with sodium hydroxide using the method of Example 1D affords the title compound.

Example 169

trans,trans-1-(2-N,N-Dibutylaminopyrimidin-4-yl)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylic acid

2-(Dibutylamino)-4-chloropyrimidine is prepared from 2,4-dichloropyrimidine according to the method of Gershon, J. Heterocyclic Chem. 24: 205 (1987) and reacted with ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate (the compound resulting from Example 6A) and diisoproplyethylamine in dioxane with heating to give the intermediate ethyl ester, which is hydrolyzed with sodium hydroxide using the method of Example 1D to the title compound.

Examples 170-266

Using the procedures described in Examples 1, 4, 5, 7, 8 and 9 and Scheme X, the following compounds can be prepared.

Ex. No.	Name
170	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(isopropylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
171	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(ethylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
172	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(1-methylpropylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
173	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
174	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(piperidinylcarbonylmethyl)-pyrrolidine-3-carboxylic acid;
175	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(1-(propylaminocarbonyl)ethyl)-pyrrolidine-3-carboxylic acid;
176	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(α-(propylaminocarbonyl)benzyl)-pyrrolidine-3-carboxylic acid;
177	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(bis-(propylaminocarbonyl)methyl)-pyrrolidine-3-carboxylic acid;
178	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(propylaminocarbonyl)ethyl)-pyrrolidine-3-carboxylic acid;
179	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminosulfonylmethyl)-pyrrolidine-3-carboxylic acid;
180	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-phenethyl)-pyrrolidine-3-carboxylic acid;
181	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(pentanoylmethyl)-pyrrolidine-3-carboxylic acid;
182	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(benzoylmethyl)-pyrrolidine-3-carboxylic acid;
183	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(hexyl)-pyrrolidine-3-carboxylic acid;
184	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-hexynyl)-pyrrolidine-3-carboxylic acid;
185	*trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propoxymethylcarbonyl-pyrrolidine-3-carboxylic acid;

186 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(phenylacetyl)-pyrrolidine-3-carboxylic acid;

187 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(anilinylcarbonyl)-pyrrolidine-3-carboxylic acid;

188 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-acetylaminoethyl)-pyrrolidine-3-carboxylic acid;

189 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-phenoxyethyl)-pyrrolidine-3-carboxylic acid;

190 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-benzodioxanylmethyl)-pyrrolidine-3-carboxylic acid;

191 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-tetrahydrofuranylmethyl)-pyrrolidine-3-carboxylic acid;

192 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(propylaminocarbonylamino)ethenyl)-pyrrolidine-3-carboxylic acid;

193 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(propylaminocarbonylamino)ethyl)-pyrrolidine-3-carboxylic acid;

194 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3-oxohex-1-enyl)-pyrrolidine-3-carboxylic acid;

195 *trans,trans*-2-(2,4-Dimethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

196 *trans,trans*-2-(2-Carboxy-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

197 *trans,trans*-2-(2-Aminocarbonyl-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

198 *trans,trans*-2-(2-Methanesulfonamido-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

199 *trans,trans*-2-(2-Aminocarbonylmethoxy-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

200 *trans,trans*-2-(2-Methoxyethoxy-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

201 *trans,trans*-2-(2-Carboxymethoxy-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

202 *trans,trans*-2-(4-Methoxy-2-tetrazolylmethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

203 *trans,trans*-2-(2-Allyloxy-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

204 *trans,trans* 2,4-Bis(4-methoxyphenyl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

205 *trans,trans* 2,4-Bis(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

206 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

207 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxole-5-yl)-1-(N-methyl-N-butylaminocarbonyl)-pyrrolidine-3-carboxylic acid;

208 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-(4-methoxyphenyl)aminocarbonyl)-3-pyrrolidine-3-carboxylic acid;

209 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-phenylaminocarbonyl)-pyrrolidine-3-carboxylic acid;

210 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-allylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

211 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

212 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-isobutylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

213 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-cyclopentylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

214 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-(2-methoxyethyl)aminocarbonyl)-pyrrolidine-3-carboxylic acid;

215 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-butoxyethylaminocarbonyl)-pyrrolidine-3-carboxylic acid;

216 *trans,trans*-2-(1,3-Benzodioxol-5-yl)-4-(4-methoxyphenyl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

217 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,4-benzodioxan-6-yl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

218 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-isopropylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

219 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-ethylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

220 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-(1-methylpropyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

221 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

222 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(1-(N-methyl-N-propylaminocarbonyl)ethyl)-pyrrolidine-3-carboxylic acid;

223 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(α-(N-methyl-N-propylaminocarbonyl)benzyl)-pyrrolidine-3-carboxylic acid;

224 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

225 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxole-5-yl)-1-(N-ethyl-N-butylaminocarbonyl)-pyrrolidine-3-carboxylic acid;

226 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-(4-methoxyphenyl)aminocarbonyl)-3-pyrrolidine-3-carboxylic acid;

227 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-phenylaminocarbonyl)-pyrrolidine-3-carboxylic acid;

228 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-allylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

229 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-isobutylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

230 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-cyclopentylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

231 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-methoxyethylaminocarbonyl)-pyrrolidine-3-carboxylic acid;

232 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-butoxyethylaminocarbonyl)-pyrrolidine-3-carboxylic acid;

233 *trans,trans*-2-(1,3-Benzodioxol-5-yl)-4-(4-methoxyphenyl)-1-(N-ethyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

234 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,4-benzodioxan-6-yl)-1-(N-ethyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

235 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-isopropylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

236 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-diethylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

237 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-(1-methylpropyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

238 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

239 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(1-(N-ethyl-N-propylaminocarbonyl)ethyl)-pyrrolidine-3-carboxylic acid;

240 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(α-(N-ethyl-N-propylaminocarbonyl)benzyl)-pyrrolidine-3-carboxylic acid;

241 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-isobutylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

242 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-cyclohexylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

243 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-dipropylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

244 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(isobutyloxyethyl)-pyrrolidine-3-carboxylic acid;

245 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(butylsulfonyl)-pyrrolidine-3-carboxylic acid;

246 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(isopropylsulfonylaminoethyl)-pyrrolidine-3-carboxylic acid;

247 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(ethoxymethylcarbonylmethyl)-pyrrolidine-3-carboxylic acid;

248 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-ethylbutyrylmethyl)-pyrrolidine-3-carboxylic acid;

249 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-(3,4-dimethoxybenzyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

250 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(1R)-1-(N-methyl-N-propylaminocarbonyl)butyl]-pyrrolidine-3-carboxylic acid;

251 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(1S)-1-(N-methyl-N-propylaminocarbonyl)butyl]-pyrrolidine-3-carboxylic acid;

252 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3-isopropoxypropyl)-pyrrolidine-3-carboxylic acid;

253 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(5-methylhexyl)-pyrrolidine-3-carboxylic acid;

254 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(5-methyl-2-hexenyl)-pyrrolidine-3-carboxylic acid;

255 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(5-methyl-4-hexenyl)-pyrrolidine-3-carboxylic acid;

256 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3,5-dimethyl-2-hexenyl)-pyrrolidine-3-carboxylic acid;

257 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-methyl-N-isobutyrylamino)ethyl)-pyrrolidine-3-carboxylic acid;

258 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-(2,2-dimethylpropyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

259 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-ethyl-N-butylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

260 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-methyl-N-benzylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

262 *trans,trans*-2-(4-Methoxyphenyl)-4-(5-indanyl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

262 *trans,trans*-2-(4-Methoxyphenyl)-4-(2,3-dihydrobenzofuran-5-yl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

263 *trans,trans*-2-(4-Methoxyphenyl)-4-(1-methylindol-5-yl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

264 *trans,trans*-2-(4-Methoxyphenyl)-4-(2-naphthyl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

265 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,2-dimethoxy-4-phenyl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

266 *trans,trans*-2-(4-Methoxyphenyl)-4-(1-methoxy-3-phenyl)-1-(N-methyl-N-propylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

Examples 267-288

Following the procedures described in Example 1 and Scheme II, the following compounds can be prepared.

267 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(propylaminocarbonylmethyl)-piperidine-4-carboxylic acid;

268 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(aminocarbonylmethyl)-piperidine-4-carboxylic acid;

269 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(4-fluorobenzyl)-piperidine-4-carboxylic acid;

270 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(2-ethoxyethyl)-piperidine-4-carboxylic acid;

271 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(2-propoxyethyl)-piperidine-4-carboxylic acid;

272 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-[2-(2-methoxyethoxy)ethyl]-piperidine-4-carboxylic acid;

273 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-[2-(2-pyridyl)ethyl]-piperidine-4-carboxylic acid;

274 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(morpholin-4-ylcarbonyl)-piperidine-4-carboxylic acid;

275 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxole-5-yl)-1-(butylaminocarbonyl)-piperidine-4-carboxylic acid;

276 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(4-methoxyphenylaminocarbonyl)-3-piperidine-4-carboxylic acid;

277 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-acetylpiperidine-3-carboxylic acid;

278 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(2-furoyl)-piperidine-3-carboxylic acid;

279 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(phenylaminocarbonyl)-piperidine-4-carboxylic acid;

280 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(allylaminocarbonylmethyl)-piperidine-4-carboxylic acid;

281 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(n-butylaminocarbonylmethyl)-piperidine-4-carboxylic acid;

282 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(N-n-butyl-N-methylaminocarbonylmethyl)-piperidine-4-carboxylic acid;

283 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(pyrrolidin-1-ylcarbonylmethyl)-piperidine-4-carboxylic acid;

284 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(isobutylaminocarbonylmethyl)-piperidine-4-carboxylic acid;

285 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(cyclopentylaminocarbonylmethyl)-piperidine-4-carboxylic acid;

286 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(morpholin-4-ylaminocarbonylmethyl)-piperidine-4-carboxylic acid;

287 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(2-phenoxyethyl)-piperidine-4-carboxylic acid;

288 *trans,trans*-3-(4-Methoxyphenyl)-5-(1,3-benzodioxol-5-yl)-1-(methoxyethylaminocarbonyl)-piperidine-4-carboxylic acid.

Example 289

trans,trans- 2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1- (4-dibutylaminophenyl)-pyrrolidine-3-carboxylic acid

4-Nitro-fluorobenzene, ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate (example 6A) and di-isopropyl ethylamine are heated in dioxane to give ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(4-nitrophenyl)-pyrrolidine-3-carboxylate. The nitro compound is hydrogenated to the corresponding aminophenyl compound. This is reacted with butyraldehyde and sodium cyanoborohydride according to the method of Borch (J. Am Chem. Soc., 93, 2897, 1971) to give the corresponding N,N-dibutylaminophenyl compound, which is hydrolyzed with sodium hydroxide using the method of example 1D to give the title compound.

Example 290

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-dibutylamino-pyrimidine-4-yl)-pyrrolidine-3-carboxylic acid

2-(Dibutylamino) 4-chloropyrimidine is prepared from 2-4-dichloropyrimidine according to the method of Gershon (J. Heterocyclic Chem. 24, 205, 1987). This compound, ethyl *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate (example 6A), and di-isopropyl ethylamine are heated in dioxane to give the intermediate ethyl ester, which is hydrolyzed with sodium hydroxide using the method of example 1D to give the title compound.

Example 291

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-butyl-N-phenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

The title compound was prepared according to the general procedure of Example 1. ^{1}H NMR (CD_3OD) : δ 0.87 (t,3H,J=8); 1.2-1.35 (m,2H); 1.35-1.5 (m,2H); 2.78 (m, 2H); 3.10 (t,1H, J=9); 3.26 (d,1H,J=15); 3.44 (dd,1H,J=5,10); 3.5-3.7 (m,3H); 3.77 (m,1H); 3.78 (s,3H); 5.93 (s,2H); 6.7-6.9 (m,4H); 7.0-7.2 (m,5H); 7.4 (m,3H). MS (DCI/NH_3): m/e 531 $(M+H)^+$. Anal calcd for $C_{31}H_{34}N_2O_6$: C, 70.17; H, 6.46; N, 5.28. Found: C,70.36; H, 6.52; N, 4.99.

Example 292

Sodium *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-*(N,N-di(n-butyl)aminocarbonylmethyl)*-pyrrolidine-3-carboxylate

Example 292A

Ethyl 3-(4-methoxyphenyl)-3-oxopropionate

Simultaneous reactions were run in both a 65-L reactor and a 35-L reactor that share the same reflux system. A nitrogen atmosphere was maintained in both. 4.0 kg (100 moles) of 60% sodium hydride in mineral oil and 32 L toluene were charged into the ambient temperature reactors. The mixture was agitated for 5 minutes and allowed to settle. 20 L of the toluene solution was aspirated. 28 L of toluene was added, agitated for 5 minutes, allowed to settle and 28 L of the toluene solution was aspirated. 68 L of toluene and 8.4 L (69.7 moles) diethyl carbonate were added. The agitation was begun and the flow of Syltherm (Note 4) in reactor jackets was initiated. A solution of 5.0 kg (33.3 moles) 4-methoxyacetophenone in 12 L toluene was added over 20 minutes. When additions were complete, the jacket temperaturewas reduced to 10° C and stirring continued for 16 hours. A solution of 6.7 L (117 moles) glacial acetic acid in 23 L deionized water was fed at the same rate that was previously used for the acetophenone solution. When addition was complete, agitation was stopped and the layers separated. The aqueous layer was washed once with 13 L toluene. The combined organic layers were washed twice with 6.7 L portions of 7% (w:w) aqueous sodium bicarbonate. The toluene solution was washed once with 6.7 L of 23% (w:w) aqueous sodium chloride . The organic solution was dried over 10 kg sodium sulfate, filtered, and the solvent removed on the rotary evaporator to provide the desired product.

Example 292B

3,4-Methylenedioxy-1-(2-nitroethenyl)-benzene

In a 45-L cryogenic reactor with a contoured, anchor stirrer was dissolved 5.537 kg (36.9 moles) piperonal in 9 L methanol and 2.252 kg (36.9 moles) nitromethane at 15°-20° C. The jacket temperature was set to -5° C and the reaction solution cooled to a temperature of

+3.5° C. A 21° C solution of 3.10 kg (38.8 moles) 50% (w:w) aqueous sodium hydroxide diluted with 3.7 L water was pumped in. The reaction temperature was maintained between 10°-15° C. When addition was complete, the jacket temperature was reset to 1° C and stirring continued for 30 minutes. A mixture of 7 kg ice in 19 L water was added to dissolve most of the solid. The reaction mixture was filtered through canvas and then a 27R10SV Honeycomb filter. The filtered solution was metered into a 21° C mixture of 7.4 L concentrated hydrochloric acid in 11.1 L deionized water. The final reaction temperature was 26° C. The resulting product was centrifuged and washed until the wash pH rose to at least 6 (by pH indicating paper). The crude product was dissolved in 92 L dichloromethane and the layers separated. The aqueous layer was washed once with 8 L dichloromethane. The combined organics were dried over 1.32 kg magnesium sulfate and filtered through Whatman #1 paper. The volume was reduced to 20% and the solution cooled to 4° C. Filtration through Whatman #1 paper, followed by ambient temperature drying *in vacuo* with an air leak afforded 1.584 kg (22%) of a first crop Concentration of the MLS to 25% followed by similar cooling, filtration, and drying afforded 0.262 kg (4%) of a second crop. The yellow product darkened on standing in light and air.

Example 292C

Ethyl 2-(4-methoxybenzoyl)-3-(1,3-benzodioxol-5-yl)-4-nitro-butanoate

Into a 45-L stirred reactor at ambient temperature were charged 5.819 kg (30.1 moles) 3,4-methylenedioxy-1-(2-nitroethenyl)-benzene and 24 L ethyl acetate . A solution of 5.355 kg (24.1 moles) ethyl 3-(4-methoxyphenyl)-3-oxopropionate in 16 L ethyl acetate was added. 280 g (275 ml, 1.84 moles) of 1,8-diaza-bicyclo[5.4.0]undec-7-ene in four equal portions was added over a 2.5 hour period. The reaction mixture was filtered through dicalite and the resulting filtered solution was used in the next step without any further purification.

Example 292D

Ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-4,5-dihydro-3H-pyrrol-3-carboxylate

The product of Example 292C (1316 ml solution consisting of 300 g Ethyl 2-(4-methoxybenzoyl)-3-(3,4-methylenedioxyphenyl)-4 nitrobutanoate in ethyl acetate) was added to a glass reactor containing RaNi # 28 (300 g). The reaction mixture was shaken under a hydrogen environment of 4 atm at room temperature for 18 hoursand filtered through a nylon 0.20 micron 47 mm millipore.

The filtrate was concentrated to 1.4 kg of dark solution and purified by normal phase silica gel chromatography eluting with 85:15, hexanes: ethyl acetate. The pure fractions were combined and concentrated (as above) until crystals formed. The solution was cooled to 0° C and filtered. The solid was washed with 2 L of 85:15, hexane: ethyl acetate (0° C). The solids

were dried *in vacuo* at 50° C to a constant weight of 193.4 g (21% yield, melting point 80-81° C) of the title compound. A further 200 g (23% yield) of product was obtained from the mother liquors.

Example 292E

Ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine 3-carboxylate

Into a 12-L flask equipped with magnetic stirring, addition funnel, temperature probe, and nitrogen inlet was charged 0.460 kg ethyl 2-(4-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4,5-dihydro-3H -pyrrole-3-carboxylate (1.25 mol). The reaction vessel was degassed with nitrogen. Absolute 3.7 L ethanol and 1.12 L of THF were added. 31 mg bromocresol green and 94.26g sodium cyanoborohydride (1.5 mol) were added. A solution containing 400 mL absolute ethanol and 200 mL of 12 M HCl was then added. The reaction mixture was stirred for 30 minutes after addition was complete. After the starting material was consumed, 0.5 L of 7% aq. $NaHCO_3$ was added. The reaction mixture was concentrated and diluted with 5 L ethyl acetate. The organic layer was washed twice with 2 L of 7% aq. $NaHCO_3$ and once with 2.5 L of 23% aq. NaCl, the dried over 190g $MgSO_4$, filtered, and concentrated to give 447 g of the title compound as a thick yellow oil.

Example 292F

Ethyl 2-(4-methoxypheny)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl) pyrrolidine 3-carboxylate

Into a 22-L flask equipped with overhead stirring, nitrogen inlet, and condenser was charged ethyl 2-(4-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)-pyrrolidine-3-carboxylate (2.223 kg,6.02 mol). The reaction vessel was degassed with nitrogen. 13.2 L ofacetonitrile, 3.66 L diisopropylethylamine (2.71 kg, 20.9 mol), and 1.567 kg dibutylamidomethyl bromide (6.26 mol) were added. The mixture was refluxed at 78° C for 17 hrs. After the disappearance of starting material , the mixture was concentrated until crystals formed. The solid was filtered and washed with 4 L ethyl acetate (0° C). Concentrating of the filtrate was continued as above until all volatiles were removed. The residue was diluted with 40 L ethyl acetate and washed with 20 L deionized water. The organic layer was washed with 8 L of 23% aq. NaCl nad dried over 0.399 kg $MgSO_4$ and filtered. Concentration as above provided 3.112 kg (96 % yield) of the title compound as a dark oil.

Example 292G

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-pyrrolidine 3-carboxylate and preparation of *trans,trans* 2-(4-methoxyphenyl)-4-(3,4-dioxyphenyl)-pyrrolidine-3-carboxylic acid ethyl ester

Into a 35-L reactor equipped with overhead stirring, nitrogen inlet, and condenser was charged 3.112 kg ethyl 2-(4-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)-pyrrolidine 3-carboxylate (5.78 mol). 16.4 L of absolute ethanol was added and the reaction vessel was degassed with nitrogen. 0.115 kg of sodium ethoxide (1.69 mol) was added and the mixture was refluxed at 79° C for 1 hr. The mixture was cooled to 15° C and 5 L of 7.6 M NaOH solution (38.1 mol) was added. The mixture was stirred at 15° C for 18 hrs. The solvent was evaporated and the residue dissolved in 15.8 L of deionized water and extracted with 28 L of ether. The ether solution was washed with 9.5 L deionized water. The aqueous wash was extracted with 3 L ether. 0.340 L of 12 M HCl was added to the aqueous layer. The aqueous layer was extracted with 24 L of ethyl acetate. The organic layer was washed with 9 L of 23% aq. NaCl, dried with 0.298 kg $MgSO_4$, filtered, and concentrated to give 2.132 kg of a dark oil. The oil was triturated with 18 L ether. The undesired solids were filtered and saved for later use. The mother liquors were concentrated to obtain 1.102 kg of light foam. The foam was dissolved in 5.5 L ethyl acetate with heating to 65° C. 14 L hexane was added slowly enough to keep the solution refluxing. The reaction mixture was cooled to 10° C and filtered. The crystals were washed with 2 L ether (0° C) and dried to constant weight *in vacuo* at 50° C to give 0.846 kg (43% yield, melting point 119-120) of crude product, which was further purified by normal phase silica gel chromatography.

Example 292H

Sodium *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl) pyrrolidine 3-carboxylate

Into a 20-L flask was charged *trans,trans* 2-(4-methoxyphenyl)-4-(3,4-methyledioxyphenyl)-1-(N,N-dibutylamino- carbonyl methyl) pyrrolidine 3-carboxylic acid (0.927 kg, 1.819 mol). A solution of 0.0720 kg NaOH (1.80 mol) dissolved in 4.65 L methanol was added. The reaction mixture was concentrated to an oil. Pentane (4 L) was added and the solution concentrated again. Pentane (4 L) was added again and concentration of this solution gave a light tan foam. The foam was dried *in vacuo* at 50° C to a constant weight of 0.937 kg (97% yield) of the title compound.

Example 293

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[decahydroisoquinolin-2-carbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1. NMR (CD_3OD, 300 MHz) shows a mixture of isomers. MS (DCI/NH_3) m/z 521. Anal calcd for $C_{30}H_{36}N_2O_6$. 1.3 TFA: C, 58.54; H, 6.62; N, 4.19 . Found: C, 58.34; H, 5.58; N, 4.00 .

Example 294

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[3,3-dimethylpiperidinyl-carbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1. NMR (CD_3OD, 300 MHz) indicates presence of rotamers. δ 0.84 (s, 3H), 0.86 (s, 3H), 1.35-1.6 (m, 4H), 3.83 (s, 3H), 5.96 (s, 2H), 6.81 (d, 1H, J=8), 6.90 (dd, 1H, J=1,8), 7.01 (d, 2H, J=9), 7.03 (s, 1H), 7.47 (d, 2H, J=9). MS (DCI/NH_3) m/z 495. Anal calcd for $C_{28}H_{34}N_2O_6$. 1.4 TFA: C, 56.55; H, 5.45; N, 4.28 . Found: C, 56.52; H, 5.83; N, 4.26 .

Example 295

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-iso-butoxycarbonylamino)ethyl]-pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods detailed in Example 61, but substituting propylamine for methylamine in Example 61B and isobutyl chloroformate for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether/ hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3H, J=7), 0.92 (m, 3H), 1.43 (h, 2H, J=7Hz), 1.7-1.9 (m, 1H), 2.72 (m, 1H), 2.90 (m, 2H), 3.10 (m, 2H), 3.25 (m, 2H), 3.40 (m, 1H), 3.55 (m, 1H), 3.62 (m, 1H), 3.7-3.9 (m, 2H) 3.78 (s, 3H), 5.95 (s, 2H), 6.72 (d, 1H, J= 8Hz), 6.82 (m, 3H), 7.00 (s, 1H), 7.30 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 527 $(M+H)^+$. Anal calcd for $C_{29}H_{38}N_2O_6 \cdot 0.5\ H_2O$: C, 65.03; H, 7.34; N, 5.23. Found: C, 65.13; H, 6.96; N, 4.95.

Example 296

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[1,2,3,4-tetrahydroisoquinolin-2- carbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1. NMR (CD_3OD, 300 MHz) indicates presence of rotamers. δ 2.97 (m, 2H), 4.68 (s, 3H), 5.97 (s, 2H), 6.83 (d, 1H, J=8), 6.9-7.0 (m, 3H), 7.03 (d, 1H, J=2), 7.1-7.3 (m, 4H), 7.4-7.5 (m, 2H). MS (DCI/NH_3) m/z 515.

Example 297

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-dimethylaminocarbonylamino)ethyl]-pyrrolidine-3-carboxylic acid

The title compound was prepared by the methods detailed in Example 61, but substituting propylamine for methylamine in Example 61B and dimethylcarbamyl chloride for isobutyryl chloride in Example 61C. The crude product was purified by preparative HPLC

(Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.70 (t, 3H, J=7), 1.28 (m, 2H), 2.75 (s, 3H), 2.82 (m, 2H), 3.1-3.45 (m, 4H), 3.70 (m, 1H), 3.80 (s, 3H), 3.90 (m, 3H), 4.72 (m, 1H), 5.95 (s, 2H), 6.75 (d, 1H, J= 8Hz), 6.87 (m, 3H), 7.05 (s, 1H), 7.40 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 498 $(M+H)^+$. Anal calcd for $C_{27}H_{35}N_3O_6 \cdot$ 1.25 TFA: C, 55.35; H, 5.71; N, 6.56. Found: C, 55.41; H, 5.71; N, 6.41.

Example 298

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(4-nitrobenzenesulfonyl)amino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Eample 66, the title compound was prepared as a yellow solid. m.p. 85-87°C. ^1H NMR (CDC13, 300 MHz) δ 0.77 (t, J=7.5Hz, 3H), 1.38 (sextet, J=7.5Hz, 2H), 2.20-2.29 (m, 1H), 2.57-2.66 (m, 1H), 2.82-3.15 (m, 4H), 3.22 (t, J=7.5Hz, 2H) 3.38 (dd, J=3Hz,J=9Hz, 1H), 3.49-3.57 (m, 1H), 3.59 (d, J=9Hz, 1H), 3.83 (s, 3H), 5.96 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.82 (dd, J=1Hz,J=8Hz, 1H), 6.87 (d, J=9Hz, 2H), 6.98 (d, J=1Hz, 1H), 7.27 (d, J=9Hz, 2H), 7.82 (d, J=9Hz, 2H), 8.23 (d, J=9Hz,2H). MS (DCI/NH3) m/e 612 $(M+H)^+$.

Example 299

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-n-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 59-61°C ^1H NMR ($CDCl_3$, 300MHz) δ 0.79 (t, J=7.5Hz, 3H), 0.90 (t, J=6Hz, 3H), 1.26-1.32 (m, 4H), 1.43 (sextet, J=7.5Hz, 2H), 1.67-1.76 (m, 2H), 2.23-2.32 (m, 1H), 2.70-3.08 (m, 7H), 3.15-3.32 (m,2H), 3.42 (dd, J=3Hz,J=9Hz, 1H), 3.52-3.57 (m, 1H), 3.63 (d, J=9Hz, 1H), 3.80 (s, 3H), 5.95 (s, 2H), 6.73 (d, J=7.5Hz, 1H), 6.83 (dd, J=1Hz,J=7.5Hz, 1H), 6.87(d, J=8Hz, 2H), 7.00 (d, J=1Hz, 1H), 7.32 (d, J=8Hz, 2H). MS (DCI/NH_3) m/e 561 $(M+H)^+$.

Example 300

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(4-trifluoromethoxybenzenesulfonyl)amino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p.122-124°C. ^1H NMR (CD3OD, 300MHz) δ 0.75 (t, J=7.5Hz, 3H), 1.26-1.45 (m, 2H), 2.96-3.08 (m, 2H), 3.23 (bs, 2H), 3.35-3.45 (m, 2H), 3.52 (t, J=10Hz, 1H), 3.81 (d, J=9Hz, 2H), 3.86 (s, 3H), 3.92 (t, J=9Hz, 1H), 4.63 (d, J=10Hz, 1H), 5.97 (s, 2H), 6.82 (d,

J=9Hz, 1H), 6.93 (dd, J=3Hz,J=9Hz, 1H), 7.06-7.08 (m, 3H), 7.46 (d, J=9Hz, 2H), 7.56 (d, J=9Hz, 2H), 7.89 (d, J=9Hz, 2H). MS (DCI/NH3), m/e 651 $(M+H)^+$.

Example 301

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(2-methyl-2-propenesulfonyl)amino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 69-71°C.. ^{1}H NMR (CDCl3, 300MHz) δ 0.79 (t, J=7.5Hz, 3H), 1.93 (sextet, J+7.5Hz, 2H), 1.92 (s, 3H), 2.25-2.35 (m, 1H), 2.68-2.77 (m, 1H), 2.85-3.28 (m, 7H), 3.40 (d, J=9Hz, 1H), 3.52-3.68 (m, 2H), 3.66 (d, J=9Hz, 1H), 3.80 (s, 3H), 4.92 (s, 1H), 5.07 (s, 1H), 5.97 (s, 2H), 6.74 (d, J=7Hz, 1H), 6.82-6.89 (m,3H), 7.01 (s,1H), 7.33 (d, J=9Hz, 2H). MS (DCI/NH3), m/e 545 $(M+H)^+$.

Example 302

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-ethylpiperidinyl-carbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1. NMR (CD_3OD, 300 MHz) shows a mixture of isomers. δ 0.75 (t, 3H, J=7), 1.4-1.7 (m, 8H), 3.84 (s, 3H), 5.96 (s, 2H), 6.83 (d, 1H, J=8), 6.91 (d, 1H, J=8), 7.0-7.1 (m, 3H), 7.52 (d, 2H, J=9). MS (DCI/NH_3) m/z 495. Anal calcd for $C_{28}H_{34}N_2O_6$. 1.6 TFA: C, 55.35; H, 5.30; N, 4.14. Found: C, 55.26; H, 5.37; N, 4.01 .

Example 303

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(2-methylpropanesulfonyl)amino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p. 72-73°C. ^{1}H NMR (CDCl3, 300 MHz) δ 0.82 (t, J=7.5Hz, 3H),1.04 (d, J=6Hz, 6H), 1.44(q, J=7.5Hz, 2H), 2.15-2.33 (m,2H), 2.57-2.75 (m, 2H), 2.84-3.08 (m, 3H), 3.12-3.21 (m, 1H), 3.23-3.45 (m, 1H), 3.43 (d, J=11Hz, 1H), 3.55-3.62 (m, 1H), 3.66 (d, J=9Hz, 1H), 3.80 (s, 3H), 5.95 (s, 2H), 6.75 (d, J=9Hz, 1H), 6.83 (dd, J=1Hz,J=9Hz, 1H), 6.87(d, J=9Hz, 2H), 7.02 (d, J=1Hz, 1H), 7.33 (d, J=9Hz, 2H). MS (DCI/NH3) m/e 547 $M+H)^+$.

Example 304

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-heptanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p.58-59°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.80(t, J=7.5Hz, 3H), 0.88 (t, J=7Hz, 3H), 1.23-1.36 (m, 8H), 1.94 (q, J=7.5Hz, 2H), 1.71(quintet, J=7Hz, 2H), 2.23-2.32 (m, 1H), 2.70-3.09(m, 7H), 3.13-3.32 (m,2H), 3.43(dd, J=3Hz,J=9Hz, 1H), 3.52-3.58(m,1H), 3.65(d, J=9Hz, 1H), 3.80 (s, 3H), 5.96(s, 2H), 6.73 (d, J=7Hz, 1H), 6.83 (dd, J=1Hz, J=7Hz, 1H), 6.87(d, J=9Hz, 2H), 7.01(d, J=1Hz, 1H), 7.32(d, J=9Hz, 2H). MS (DCI/NH_3) m/e 589 M+H)$^+$.

Example 305

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-ethyl-N-ethoxycarbonylamino)ethyl]-pyrrolidine-3-carboxylic acid

Prepared by the methods detailed in Example 61, but substituting ethylamine for methylamine in Example 61B and ethyl chloroformate for isobutyryl chloride in Example 61C. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, J=7), 1.22 (m, 3H), 3.0-3.2 (m, 4H), 3.42 (m, 2H), 3.78 (s, 3H), 3.82 (m, 4H), 4.10 (q, 2H, J=7Hz), 3.5 (br s, 1H), 5.97 (dd, 2H, J=1,7Hz), 6.72 (d, 1H, J= 8Hz), 6.84 (m, 3H), 7.00 (s, 1H), 7.42 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 485 (M+H)$^+$. Anal calcd for $C_{26}H_{32}N_2O_7 \cdot 1.2$ TFA: C, 54.90; H, 5.39; N, 4.51. Found: C, 55.01; H, 5.36; N, 4.56.

Example 306

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-hexanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p.59-60°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.80(t, J=7.5Hz,3H), 0.89(t, J=7Hz, 3H), 1.25-1.36(m, 6H), 1.53(sextet, J=7.5Hz, 2H), 1.72(quintet, J=7Hz, 2H), 2.23-2.32(m, 1H), 2.72-3.08(m, 7H), 3.15-3.32(m, 2H), 3.43(d, J=9Hz, 1H), 3.55-3.62(m, 1H), 3.65 (d, J=10Hz, 1H), 3.80(s, 3H), 5.96(s, 2H), 6.74(d, J=7.5Hz,1H), 6.82(d, J=7.5Hz,1H), 6.87(d, J=9Hz, 2H), 7.01(s,1H), 7.32(d, J=9Hz,2H). MS (DCI/NH_3), m/e 575 (M+H)$^+$.

Example 307

trans-trans-2-(4-Ethylphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-di(n-butyl)aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in examples 1 and 49, substituting ethyl 4-ethylbenzoylacetate (prepared by the method of Krapcho et al., Org.

Syn. 47, 20 (1967) starting with 4'-ethylacetophenone) in procedure 49B. NMR ($CDCl_3$, 300 MHz) δ 7.31 (2H, d, J=8Hz), 7.16 (2H, d, J=8Hz), 7.03 (1H, d, J=3Hz), 6.86 (1H, dd, J=8&3Hz), 6.73 (1H, d, J=9Hz), 5.94 (1H, d, J=4Hz), 5.92 (1H, d, J=4Hz), 3.77 (1H, d, J=9Hz), 3.60 (1H, m), 3.53-3.23 (5H, m), 3.13-2.90 (4H, m), 2.73 (1H, d, J=14Hz), 2.62 (2H, q, J=9Hz), 1.45 (2H, m), 1.40-1.10 (6H, m), 1.02 (2H, m), 0.87 (3H, t, J=7Hz), 0.78 (3H, t, J=7Hz). m/e (DCI, NH_3) 509 (MH^+) Anal.calc. for $C_{30}H_{40}N_2O_5$ C 70.84, H 7.93, N 5.51. Found C 70.80, H 7.85, N 5.25 .

Example 308

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-(2-chloroethoxy)carbonylamino)ethyl]-pyrrolidine-3-carboxylic acid

Prepared by the methods detailed in Example 61, but substituting propylamine for methylamine in Example 61B and 2-chloroethyl chloroformate for isobutyryl chloride in Example 61C. The crude product was purified by trituration with 1:1 diethyl ether/ hexane. The resulting solid was dissolved in CH_3CN and water and lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3H, J=7), 1.22 (m, 3H), 2.15 (m, 1H), 2.75 (m, 1H), 2.85 (m, 1H), 3.1 (m, 2H), 3.25 (m, 2H), 3.5 (m, 3H), 3.65 (m, 2H), 3.80 (s, 3H), 4.18 (m, 1H), 4.30 (m, 1H), 5.98 (s, 2H), 6.72 (m, 1H), 6.82 (m, 3H), 7.00 (m, 1H), 7.30(m, 2H). MS (DCI/NH_3) m/e 533 $(M+H)^+$. Anal calcd for $C_{27}H_{33}N_2O_7Cl$: C, 60.84; H, 6.24; N, 5.26. Found: C, 60.48; H, 6.04; N, 5.10.

Example 309

trans-trans-2-(2-Methoxyethyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-di(n-butyl)aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1, substituting ethyl 5-methoxy-3-oxopentanoate for ethyl 4-methoxybenzoylacetate in Example 1A. The title compound is a yellow foam. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J=7Hz) and 0.95 (t, J=7Hz, 6H total), 1.28-1.41 (br m, 4H), 1.45-1.63 (br m, 4H), 2.00-2.20 (br m, 2H), 3.06 (br t, J=9Hz, 1H), 3.30 (s) and 3.20-3.68 (br m, 11H total), 3.72-4.10 (br m, 4H), 5.92 (s, 2H), 6.72 (d, J=8.5Hz, 1H), 6.82 (dd, J=1.5, 8.5Hz, 1H), 6.91 (d, J=1.5Hz, 1H); MS (FAB) m/e 463 $(M+H)^+$. Anal calcd for $C_{25}H_{38}N_2O_5 \cdot H_2O$: C, 62.48; H, 8.39; N, 5.83. Found: C, 62.13; H, 8.15; N, 5.69.

Example 310

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-ethyl-N-n-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was prepared as a white solid. m.p.57-58°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.89(t, J=7Hz, 3H), 1.06(t, J=7.5Hz, 3H), 1.26-1.37(m, 4H), 1.72(quintet, J=7.5Hz, 2H), 2.22-2.32(m,1H), 2.71-2.96(m,5H), 3.08-3.30(m,4H), 3.95(d, J=9Hz, 1H), 3.53-3.60(m, 1H), 3.67(d, J=9Hz,1H), 3.80(s, 1H), 5.97(s, 2H), 6.73(d, J=9Hz, 1H), 6.82(d, J=9Hz,1H), 6.88(d, J=9Hz, 2H),7.02(s,1H), 7.33(d, J=9Hz, 2H). MS (CDI/NH_3) m/e 547 $(M+H)^+$.

Example 311

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-dicyclohexylamino carbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1. NMR (CD_3OD, 300 MHz) δ 1.0-2.0 (m, 20H), 3.0-3.1 (m, 2H), 3.80 (s, 3H), 5.95 (s, 2H), 6.75 (d, 1H, J=8), 6.86 (dd, 1H, J=2,8), 6.95 (d, 2H, J=9), 7.04 (d, 1H, J=2), 7.38 (d, 2H, J=9). MS (DCI/NH_3) m/z 563. Anal calcd for $C_{33}H_{42}N_2O_6$. 0.5 H_2O: C, 69.33; H, 7.58; N, 4.90 . Found: C, 69.42; H, 7.29; N, 4.78.

Example 312

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-tert-butoxycarbonylamino)ethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 61, substituting propylamine for aqueous methylamine in Example 61B and di-tert-butyldicarbonate for isobutyryl chloride in Example 61C. NMR (CD_3OD, 300 MHz) suggests presence of rotamers δ 0.81 (t, 3H, J=7), 1.2-1.5 (m, 11H), 3.78 (s, 3H), 5.92 (dd, 2H, J=1,2), 6.74 (d, 1H, J=8), 6.84 (dd, 1H, J=2,8), 6.92 (d, 2H, J=9), 6.99 (bd s, 1H), 7.35 (d, 2H, J=9). MS (DCI/NH_3) m/z 527. Anal calcd for $C_{29}H_{38}N_2O_7$: C, 66.14; H, 7.27; N, 5.32 . Found: C, 66.,05; H, 7.36; N, 5.15.

Example 313

trans-trans-2-(4-Methoxy-3-fluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-di(n-butyl)aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the methods described in examples 1 and 43, using 4-methoxy-3-fluoro acetophenone in place of 4-methoxy acetophenone. m.p. 142-143 °C. NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J=7Hz, 3H), 0.88 (t, J=7Hz, 3H), 1.03-1.50 (m, 8H), 2.82 (d, J=13Hz, 1H), 2.90-3.13 (m, 4H), 3.20-3.50 (m, 3H), 3.39 (d, J=13H, 1H), 3.55-3.65 (m, 1H), 3.82 (d, J=10Hz, 1H), 3.87 (s, 3H), 5.91 (dd, J=2Hz, 4Hz, 2H), 6.72 (d, J=8Hz, 1H), 6.83-6.91 (m, 2H), 6.99 (d, J=2Hz, 1H), 7.06 (m, 2H). Anal calcd for $C_{29}H_{37}N_2O_6F$: C, 65.89; H, 7.06; N, 5.30 . Found: C, 65.82; H, 7.13; N, 5.29.

Example 314

trans,trans-2-(Propyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid

Example 314A

Propyl pentanesulfonamide

Pentane sulfonyl chloride (687 mg, 4.03 mmol) was dissolved in 5 mL CH_2Cl_2 and added to an ice-cooled solution of n-propylamine (0.40 mL, 4.82 mmol) and ethyldiisopropylamine (0.85 mL, 4.88 mmol) in 5 mL CH_2Cl_2 under a nitrogen atmosphere. The reaction was stirred at 0 °C for 30 min, then at 25 °C for 4 h. The solution was partitioned between 20 mL of 1.0 M aqeous $NaHSO_4$ and 25 mL CH_2Cl_2. The organic phase was washed sequentially with 25 mL H_2O and 25 mL brine, then dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 739 mg (3.83 mmol, 95%) of the title compound as a white solid. TLC (25% EtOAc-hexane) Rf 0.23; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J=7Hz, 3H), 0.97 (t, J=7Hz, 3H), 1.28-1.50 (br m, 4H), 1.52-1.68 (m, 2H), 1.75-1.90 (br m, 2H), 2.98-3.06 (m, 2H), 3.08 (q, J=6Hz, 2H), 4.10-4.23 (br m, 1H); MS (DCI/NH_3) m/e 211 $(M+NH_4)^+$.

Example 3149B

Ethyl *trans,trans*--4-(1,3-benzodioxol-5-yl)-1-(2-bromoethyl)-2-propylpyrrolidine-3-carboxylate

The title compound was prepared according the procedure of Example 61A, substituting the compound of Example 94B for the pyrrolidine mixture.

Example 314C

Ethyl*trans,trans*-2-(Propyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylate

A solution of the compound of Example 314A (6.6 mg, 34 μmol) in 0.1 mL DMF was treated with sodium hydride (2 mg, 60% oil dispersion, 1.2 mg NaH, 50 μmol). The resulting mixture was stirred at room temperature for 15 min, then a solution of the compound of Example 189B (9.0 mg, 22 μmol) in 0.1 mL DMF was added, followed b y 0.5 mg of tetra-n-butylammonium iodide. The reaction was sealed under argon and stirred at 60 °C overnight. The reaction was concentrated under high vacuum, and the residue was partitioned between 2 mL of saturated aqueous $NaHCO_3$, 1 mL water and 5 mL EtOAc. The organic phase was washed with 1 mL brine, dried by passing through a plug of Na_2SO_4, and the filtrate

concentrated in vacuo to an oil. The crude product was purified by preparative TLC (silica gel, 8 x 20 cm, 0.25 mm thickness, eluting with 20% EtOAc-hexane, providing 8.4 mg (73%) of the title compound as a wax.

Example 314D

trans,trans-4-(1,3-benzodioxol-5-yl)-2-(Propyl)-1-(2-(N-propyl-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid

The title compound was prepared according to the procedure of Example 71C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88-1.00 (m, 9H), 1.20-1.55 (br m, 6H), 1.55-1.68 (m, 3H), 1.70-1.85 (br m, 2H), 1.90-2.16 (br m, 2H), 2.84-3.26 (br m, 6H), 3.26-3.90 (br m, 6H), 5.95 (s, 2H), 6.76 (d, J=8Hz, 1H), 6.79 (m, 1H), 6.93 (br s, 1H); HRMS (FAB) calcd for $C_{25}H_{41}N_2O_6S$ $(M+H)^+$ 497.2685, found 497.2679.

Example 315

trans,trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-dimethylsulfamoylamino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 66, the title compound was preapred as a white solid. m.p.59-61°C. ^{1}H NMR (CDCl3, 300MHz) δ 0.79 (t, J=7.5Hz, 3H), 1.45(sextet, J=7.5Hz, 2H), 2.22-2.31(m,1H), 2.65(s, 6H), 2.70-2.79(m, 1H), 2.85-3.04(m, 4H), 3.09-3.32(m, 2H), 3.40(d, J=9Hz, 1H),3.55 (t, J=9Hz,1H), 3.65(d, J=9Hz,1H), 3.81(s, 3H), 5.96(s,2H), 6.75(d, J=9Hz, 1H), 6.83(d, J=9Hz, 1H), 6.88(d, J=9Hz, 2H), 7.02(s, 1H), 7.34(d, J=9Hz, 2H). MS (DCI/NH3) m/e534 $(M+H)^+$.

Example 316

trans-trans-2-(4-Methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-[4-methoxyphenyl]sulfonylamino)propyl]-pyrrolidine-3-carboxylic acid

Example 316A

Ethyl *trans-trans* and *cis-trans* 2-(4-Methoxyphenyl)-4-(1,3-benzodiox-5-yl) -1-(3-bromopropyl) pyrrolidine-3-carboxylate

A 2:1 mixture of *trans-trans* and *cis-trans* ethyl 2-(4-methoxyphenyl)-4-(1,3-benzodiox-5-yl) -pyrrolidine-3-carboxylate (4.00 g; prepared according to example 1C), 32 ml dibromopropane, and 200 mg sodium iodide, were heated at 100° for 1.25 hrs. The excess dibromopropane was removed in vacuo and the residue was dissolved in toluene. After shaking with potassium bicarbonate, the solution was dried (Na_2SO_4) and the solution concentrated. The residue was chromatographed on silica gel eluting with 5:1 hexane:EtOAc. yielding 5.22 (98%) of the title compound.

Example 316B

Ethyl *trans-trans* and *cis-trans* 2-(4-Methoxyphenyl)-4-(1,3-benzodiox-5-yl) -1-(3-propylaminopropyl) pyrrolidine-3-carboxylate

The compound described in Example 316A (5.22 g) was heated at 80° for 2 hrs.with 35 ml. ethanol, 2.5 g. propylamine and 35 mg. sodium iodide. The solvents were removed in vacuo. The residue was dissolved in toluene, shaken with potassium bicarbonate solution and dried (Na_2SO_4). The soilution was concentated in vacuum to give 4.96 g of the title compound as an orange oil. This was used in the next step without purification.

Example 316C

trans-trans-2-(4-Methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-[4-methoxyphenyl]sulfonylamino)propyl]-pyrrolidine-3-carboxylic acid

Using the method described in example 66, the compound prepared in Example 316B was reacted with 4-methoxybenzenesulfonyl chloride in acetonitrile containing diisopropylethylamine. The resulting product was chromatographed on silica gel (30% EtOAc in hexane), and hydrolyzed to the title compound by the method of example 1D. NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, J=7Hz, 3H), 1.40-1.52 (m, 2H), 1.56-1.70 (m, 2H), 2.00-2.11 (m, 1H), 2.40-2.51 (m, 1H), 2.69-2.78 (m, 1H), 2.84-3.03 (m, 4H), 3.19-3.34 (m, 2H), 3.48-3.59 (m, 2H), 3.80 (s, 3H), 3.86 (s, 3H), 5.95 (s, 2H), 6.74 (d, J=8Hz, 1H), 6.85 (d, J=8Hz, 3H), 6.93 (d, J=8Hz, 2H), 7.02 (d, J=2Hz, 1H), 7.29 (d, J=8Hz, 2H), 7.69 (d, J=8Hz, 2H). Anal calcd for $C_{32}H_{38}N_2O_8S$: C, 62.93; H, 6.27; N, 4.59. Found: C, 62.97; H, 6.39; N, 4.45.

Example 317

trans-trans-2-(4-Methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-propylsulfonylamino)propyl]-pyrrolidine-3-carboxylic acid

Using the method described in example 66, the propylamino compound prepared in Example 316B was reacted with propanesulfonyl chloride in acetonitrile containing diisopropylethylamine. The resuling product was chromatographed on silica gel (30% EtOAc in hexane) and hydrolyzed to the title compound by the method of example 1D. NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J=7Hz, 3H), 1.02 (t, J=7Hz, 3H), 1.47-1.60 (m, 2H), 1.65-1.85 (m, 4H), 2.04-2.16 (m, 1H), 2.42-2.57 (m, 1H), 2.72-3.11 (m, 5H), 3.25-3.41 (m, 2H), 3.50-3.62 (m, 2H), 3.80 (s, 3H), 5.85 (s, 2H), 6.72 (d, J=8Hz, 1H), 6.80-6.90 (m, 3H), 7.02 (d, J=2Hz, 1H), 7.30 (d, J=9Hz, 2H). Anal calcd for $C_{28}H_{38}N_2O_7S$: C, 61.52; H, 7.01; N, 5.12 . Found: C, 61.32; H, 7.01; N, 5.01.

Example 318

trans,trans--2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)1-(2-(N-propyl-N-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 313 and Example 66, the title compound was prepared as a white solid. m.p.66-68°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.81(t,J=7.5Hz, 3H), 0.89(t, J=7Hz, 3H), 1.26-1.35(m, 4H), 1.45(sextet, J=7.5Hz, 2H), 1.68-1.76(m, 2H), 2.25-2.33(m, 1H), 2.72-2.92(m, 5H), 2.97-3.12(m, 2H), 3.16-3.33(m,2H), 3.43(dd, J=3Hz,J=9Hz,1H), 3.53-3.60(m, 1H), 3.66(d, J=10Hz, 1H), 3.88(s, 3H), 5.95(s, 2H), 6.74(d, J=8Hz, 1H), 6.82(dd, J=1Hz,J=8Hz,1 H), 6.92(t, J=8Hz,1H), 6.97(d, J=1Hz, 1H), 7.12(d, J=8Hz, 1H), 7.18(dd, J=1Hz,J=12Hz, 1H). MS (DCI/NH_3) m/e 579 $(M+H)^+$.

Example 319

trans-trans-2-(4-Pyridinyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-di(n-butyl)aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the methods described in examples 1 and 43, using methyl 3-oxo-3-(4-pyridyl)propanoate (J. Am. Chem. Soc. **1993**, *115*, 11705) in place of ethyl (4-methoxybenzoyl)acetate. m.p. 131-132 °C. NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J+7Hz, 3H), 0.88 (t, J=7Hz, 3H), 1.05-1.50 (m, 8H), 2.90 (dd, J= 7Hz, 9Hz, 1H), 2.97 (d, J=13Hz, 1H), 3.00-3.25 (m, 4H), 3.32 (m, 1H), 3.39 (d, J=13Hz, 1H), 3.45-3.52 (m, 1H), 3.67-3.78 (m, 1H), 4.10 (d, J=9Hz, 1H), 5.92 (dd, J=2Hz, 4 Hz, 2H), 6.75 (d, J=9Hz, 1H), 6.90 (dd, J=9Hz, 2Hz, 1H), 7.02 (d, J=2Hz, 1H), 7.45 (d, J=8Hz, 2H), 8.50 (d, J=8Hz, 2H). Anal calcd for $C_{27}H_{35}N_3O_5$: C, 67.34; H, 7.33; N, 8.73 . Found: C, 67.39; H, 7.45; N, 8.61.

Example 320

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(N-propyl-N-diethylaminocarbonylamino)ethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 61, substituting propylamine for aqueous methylamine in Example 61B and diethylcarbamyl chloride for isobutyryl chloride in Example 61C. NMR (CD_3OD, 300 MHz) δ 0.74 (t, 3H, J=7), 1.09 (t, 6H, J=7), 1.33 (m, 2H), 3.17 (q, 4H, J=7), 3.78 (s, 3H), 4.04 (m, 1H), 5.93 (s, 2H), 6.86 (d, 1H, J=8), 7.06 (dd, 1H, J=2,8), 6.94 (d, 2H, J=9), 7.04 (d, 1H, J=2), 7.40 (d, 2H, J=9). MS (DCI/NH_3) m/z 526. Anal calcd for $C_{29}H_{39}N_3O_6$. 0.1 TFA: C, 65.31; H, 7.34; N, 7.82 . Found: C, 65.33; H, 7.43; N, 8.14.

Example 321

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[3,5-dimethylpiperidinyl-carbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1. NMR (CD_3OD, 300 MHz) shows mixture of isomers. δ 0.88 (d, 3H, J=7), 0.93 (d, 3H, J=7), 3.82 (s, 3H), 5.95 (s, 2H), 6.82 (d, 1H, J=8), 6.89 (dd, 1H, J=1,8), 7.00 d, 2H, J=9), 7.03 (m, 1H), 7.47 (d, 2H, J=9). MS (DCI/NH_3) m/z 495.

Example 322

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-di(s-butyl)aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1. NMR (CD_3OD, 300 MHz) suggests a mixture of isomers. δ 0.83 (t, 6H, J=8), 1.27 (d, 6H, J=7), 1.6 (m, 2H), 3.79 (s, 3H), 5.93 (s, 2H), 6.75 (d, 1H, J=8), 6.86 (d, 1H, J=8), 6.94 (d, 2H, J=9), 7.03 (d, 1H, J=2), 7.35 (d, 2H, J=9). MS (DCI/NH_3) m/z 511.

Example 323

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N-(2-Methylphenyl)-N-butylamino carbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1. MS (DCI/NH_3) m/z 545. Anal calcd for $C_{32}H_{36}N_2O_6$. 0.9 H_2O: C, 68.53; H, 6.79; N, 4.99 . Found: C, 68.56; H, 6.62; N, 4.71.

Example 324

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N-(3-Methylphenyl)-N-butylamino carbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared using the procedures described in example 1. NMR (CD_3OD, 300 MHz) d 0.88 (t, 3H, J=7), 1.2-1.5 (m, 4H), 2.31 (s, 3H), 2.8 (m, 2H), 3.14 (t, 1H, J=10), 3.3 (m, 1H), 3.44 (dd, 1H, J=5,10), 3.53 (m, 1H), 3.60 (t, 2H, J=7), 3.79 (s, 3H), 3.82 (m, 1H), 5.93 (s, 2H), 6.74 (d, 1H, J=8), 6.8-6.9 (m, 5H), 7.06 (d, 1H, J=2), 7.09 (d, 2H, J=9), 7.18 (d, 1H, J=7), 7.27 (t, 1H, J=7). MS (DCI/NH_3) m/z 545. Anal calcd for $C_{32}H_{36}N_2O_6$. 0.8 H_2O: C, 68.75; H, 6.78; N, 5.01 . Found: C, 68.70; H, 6.67; N, 4.85.

Example 325

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(benzyloxymethyl)-1-((N,N-dibutylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 325A

Ethyl *trans,trans*-4-(1,3-Benzodioxol-5-yl)-2-(benzyloxymethyl)-1-((N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The procedures of Example 1A-1D were followed, substituting ethyl 4-benzyloxy-3-oxobutyrate for 4-methoxybenzoylacetate in Example 1A, to afford the title compound as a colorless oil. TLC (30% EtOAc-hexane) Rf 0.18; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J=7Hz, 6H), 1.17 (t, J=7Hz, 3H), 1.20-1.34 (br m, 4H), 1.40-1.56 (br m, 3H), 2.85 (t, J=8Hz, 1H), 2.98-3.30 (m, 5H), 3.39-3.60 (m, 3H), 3.64-3.75 (m, 2H), 3.92 (d, J-14Hz, 1H), 4.10 (two overlapping q, J=6.5Hz, 2H), 4.53 (s, 2H), 5.91 (m, 2H), 6.69 (d, J=9Hz, 1H), 6.77 (dd, J=1.5, 9Hz, 1H), 6.91 (d, J=1.5Hz, 1H); MS (DCI/NH_3) m/e 553 $(M+H)^+$.

Example 325B

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(benzyloxymethyl)-1-((N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The title compound was prepared according to the procedure of Example 71C, as a colorless glass. TLC (5% MeOH-CH_2Cl_2) Rf 0.13; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J=7Hz), and 0.90 (t, J=7Hz, 6H total), 1.15-1.52 (br m, 8H), 2.96-3.35 (br m, 5H), 3.50-3.75 (br m, 2H), 3.80 (dd, J=3, 13Hz, 1H), 3.88-4.40 (br m, 6H), 4.45 (AB, 2H), 5.90 (s, 2H), 6.70 (d, J=8Hz, 1H), 6.84 (dd, J=1,8Hz, 1H), 6.93 (d, J=1Hz, 1H), 7.28-7.39 (m, 5H); MS (DCI/NH_3) m/e 524 $(M+H)^+$.

Example 326

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(hydroxymethyl)-1-((N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 326A

Ethyl*trans,trans*-4-(1,3-Benzodioxol-5-yl)-2-(hydroxymethyl)-1-((N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The resultant product from Example 325A (128 mg, 0.232 mmol) and 25 mg of 20% $Pd(OH)_2$ on charcoal in 7 mL EtOH was stirred under 1 atm hydrogen for 48 h. The mixture was filtered through a plug of celite, and the catalyst was washed with 2 x 10 mL EtOH, then the combined filtrate and washes were concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (40%EtOAc-hexane) provided the title compound.

Example 326B

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(hydroxymethyl)-1-((N,N-di(butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The title compound was prepared according to the procedure of Example 71C.

Example 327

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(N-methylpropenamid-3-yl)-1-((N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 327A

Ethyl *trans,trans*--4-(1,3-Benzodioxol-5-yl)-2-(formyl)-1-((N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The title compound is made by selective oxidation (e.g. using the Swern oxidation with DMSO, oxalyl chloride, ethyldiisopropylamine or using the Dess-Martin periodinane) of the compound of Example 326A.

Example 327B

Ethyl *trans,trans*--4-(1,3-Benzodioxol-5-yl)-2-(O-tert-butylpropenoat-3-yl)-1-((N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The title compound is produced by condensing the compound of Example 327A with tert-butyl triphenylphosphoranylidine acetate in CH_2Cl_2 solution.

Example 327C

Ethyl *trans,trans*--4-(1,3-Benzodioxol-5-yl)-2-(propenoic acid-3-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The title compound is produced by reacting the compound of Example 327B with trifluoacetic acid in CH_2Cl_2 (1:1).

Example 327D

Ethyl *trans,trans*--4-(1,3-Benzodioxol-5-yl)-2-(N-methylpropenamid-3-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The title compound is produced by condensing the compound of Example 327C with methylamine hydrochloride in the presence of a carbodiimide (e.g. N-ethyl-N-(3-dimethylamino)propylcarbodiimide, DCC).

Example 327E

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(N-methylpropenamid-3-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The title compound is produced by reacting the compound of Example 327D with lithium hydroxide according to the procedure of Example 71C.

Example 328

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(1-hydroxy-2-propen-3-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 328A

Ethyl *trans,trans*--4-(1,3-Benzodioxol-5-yl)-2-(1-hydroxy-2-propen-3-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The title compound is produced by reacting the compound of Example 327C with borane methyl sulfide complex.

Example 328B

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(1-hydrox-2-propen-3-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The title compound is produced by condensing the compound of Example 328A with lithium hydroxide according to the procedure of Example 71C.

Example 329

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(N-benzylaminomethyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 329A

Ethyl *trans,trans*--4-(1,3-Benzodioxol-5-yl)-2-(N-benzylaminomethyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The title compound is produced by condensing the compound of Example 327A with benzylamine in the presence of sodium cyanoborohydride in ethanol.

Example 329B

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(N-benzylaminomethyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The title compound is produced by reacting the compound of Example 329A with lithium hydroxide according to the procedure of Example 71C.

Example 330

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(N-acetyl-N-benzylaminomethyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 330A

Ethyl *trans,trans*--4-(1,3-Benzodioxol-5-yl)-2-(N-acetyl-N-benzylaminomethyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The title compound is produced by reacting the compound of Example 3294A with acetic anhydride in the presence of pyridine or triethylamine.

Example 330B

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(N-acetyl-N-benzylaminomethyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The title compound is produced by reacting the compound of Example 330A with lithium hydroxide according to the procedure of Example 71C.

Example 331

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(ethynyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 331A

Ethyl *trans,trans*--4-(1,3-Benzodioxol-5-yl)-2-(ethynyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The title compound is made by employing the procedure of Corey and Fuchs (Tetrahedron Lett. **1972**, 3769-72), using the compound of Example 327A.

Example 331B

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(ethynyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The title compound is produced by reacting the compound of Example 331A with lithium hydroxide according to the procedure of Example 71C.

Example 332

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(1-pentynyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Example 332A

Ethyl *trans,trans*--4-(1,3-Benzodioxol-5-yl)-2-(pentynyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate

The title compound is made by palladium-catalyzed coupling of the compound of Example 206A and propyl iodide, employing the procedure of Taylor, et. al. (J. Org. Chem. **1989**, 54(15), 3618-24).

Example 332B

trans,trans--4-(1,3-Benzodioxol-5-yl)-2-(1-pentynyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

The title compound is produced by reacting the compound of Example 332A with lithium hydroxide according to the procedure of Example 71C.

Example 333

trans-trans-2-(4-Methoxphenyl)-4-(1,3-benzodioxol-5-yl)-1-[2-(2,6-dioxopiperidinyl) ethyl}-pyrrolidine-3-carboxylic acid

The compound of example 61A is added to a solution of the sodium salt of glutarimide in dimethylformamide. After stirring 24 hours, water is added and the mixture is extracted with ether. The resultant glutarimide is hydrolyzed to the title compound by the method of example 1D.

Example 334

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-diphenylaminocarbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared according to the procedures described in Example 1. ^1H NMR (300 MHz, CD_3OD) δ 2.83 (dd, 1, J = 8.1, 9.7), 2.99 (d, 1, J = 15.4), 3.19 (t, 1, J = 9.5), 3.49 (d, 1, J = 15.3), 3.51 (dd, 1, J = 4.6, 9.5), 3.57 (m, 1), 3.79 (s, 3), 3.85 (d, 1, J = 9.5), 5.90 (s, 2), 6.71 (d, 1, J = 8.0), 6.84 (m, 3), 7.04 (d, 1, J = 1.6), 7.14-7.16 (m, 6), 7.19-7.34 (m, 6); MS (DCI/NH_3) m/z 551; Anal Calcd for $C_{33}H_{30}N_2O_6 \cdot 0.65H_2O \cdot 0.35C_2H_5OCOCH_3$: C, 69.77, H, 5.77, N, 4.76. Found: C, 69.75, H, 5.55, N, 4.64.

Example 335

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[N,N-diisopropylaminocarbonylmethyl]-pyrrolidine-3-carboxylic acid.

The title compound was prepared according to the procedures described in Example 1. ^1H NMR (300 MHz, CD_3OD) δ 0.95 (d, 3, J = 6.5), 1.24 (d, 3, J = 6.4), 1.30 (d, 6, J = 6.8), 2.85 (d, 1, J = 12.5), 3.04 (dd, 1, J = 8.1, 9.8), 3.14 (t, 1, J = 9.7), 3.32-3.55 (m, 3), 3.63 (m, 1), 5.92 (s, 2), 6.75 (d, 1, J = 8.1), 6.85 (dd, 1, J = 1.7, 8.1), 6.93 (m, 2), 7.02 (d, 1, J = 1.7), 7.35 (m, 2). MS (DCI/NH_3) m/z 483. Anal Calcd for $C_{27}H_{34}N_2O_6 \cdot 0.65$ EtOAc: C, 65.86, H, 7.32, N, 5.19. Found: C, 5.74, H, 7.26, N, 5.52.

Example 336

trans,trans-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-N-propyl-N-butanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 313 and Example 66, the title compound was prepared as a white solid. m.p.65-66°C. ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.82(t, J=7.5Hz, 3H), 0.92(t, J=7.5Hz, 3H), 1.34-1.52(m, 4H), 1.72(quintet, J=7.5Hz,2H), 2.25-2.35(m,1H), 2.72-2.94(m, 5H), 2.97-3.12(m, 2H), 3.19-3.46(m, 2H), 3.44(d, J=9Hz,1H), 3.53-3.60(m, 1H), 3.67(d, J=9Hz, 1H), 3.89(s, 3H), 5.95(s, 2H), 6.74(d, J=8Hz, 1H), 6.82(d, J=8Hz, 1H), 6.92(t, J=9Hz, 1H), 6.97(s, 1H), 7.12(d, J=9Hz, 1H), 7.18(d, J=12Hz, 1H). MS (DCI/NH_3) m/e 565 $(M+H)^+$.

Example 337

Using methods described in the above examples, the compounds disclosed in Table 1 can be prepared.

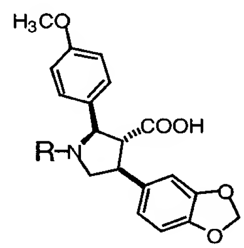


Table 1

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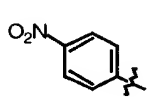	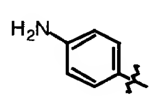	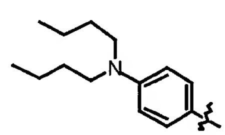
1.	2.	3.

Table 1 cont.

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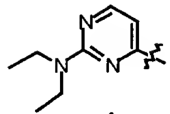

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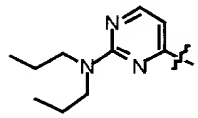

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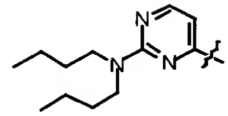

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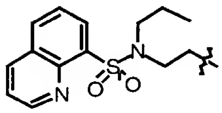

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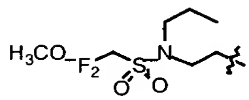

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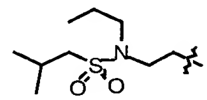

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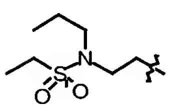

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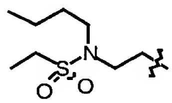

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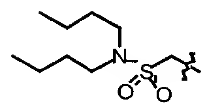

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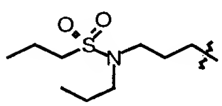

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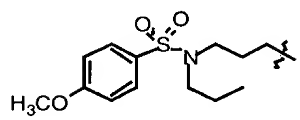

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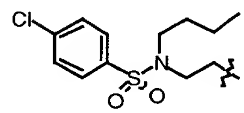

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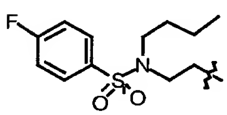

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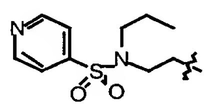

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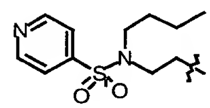

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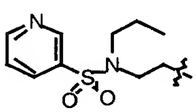

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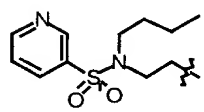

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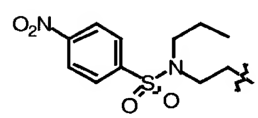

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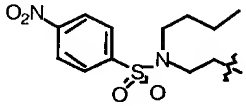

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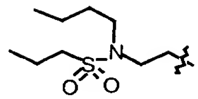

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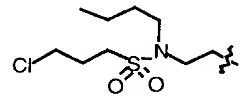

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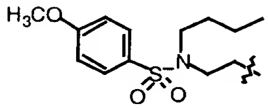

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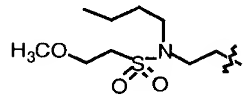

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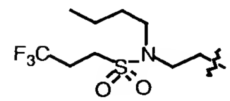

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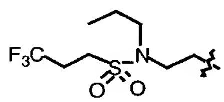

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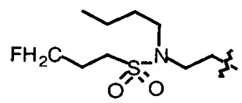

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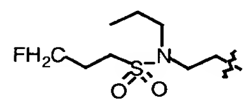

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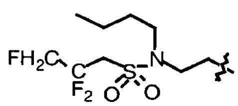

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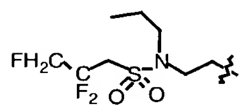

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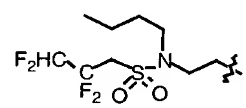

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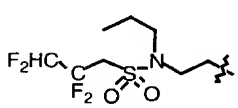

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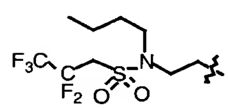

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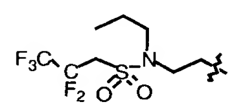

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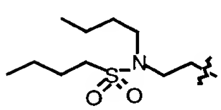

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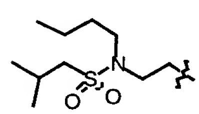

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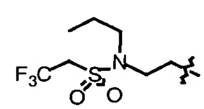

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Table 1 cont.

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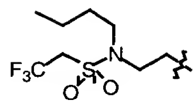
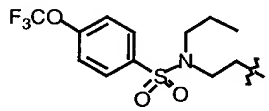
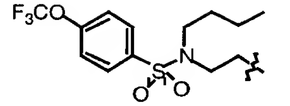
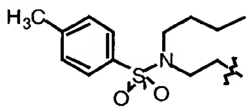
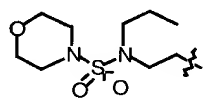
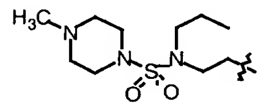
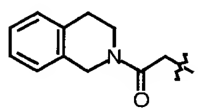
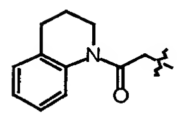
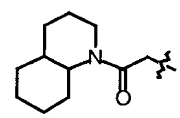
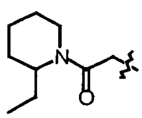
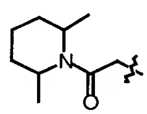
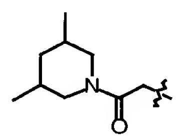
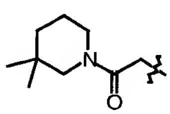
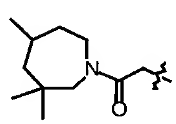
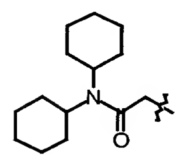
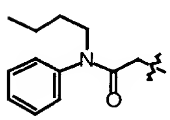
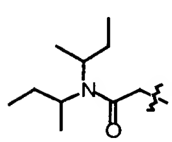
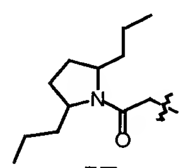
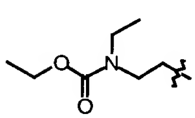
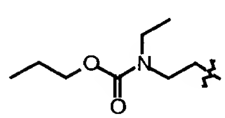
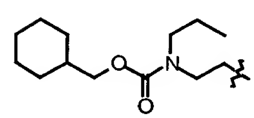
 40.	 41.	 42.
 43.	 44.	 45.
 46.	 47.	 48.
 49.	 50.	 51.
 52.	 53.	 54.
 55.	 56.	 57.
 58.	 59.	 60.

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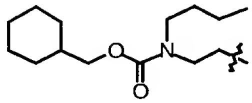
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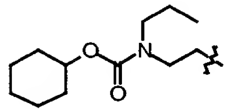
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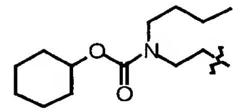
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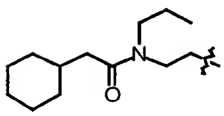
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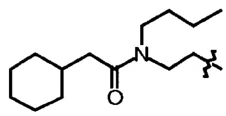
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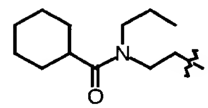
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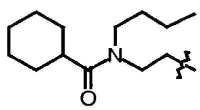
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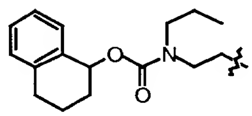
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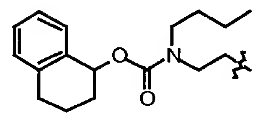
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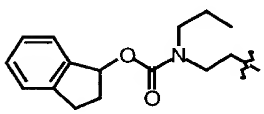
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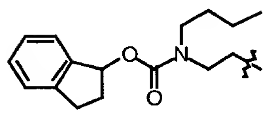
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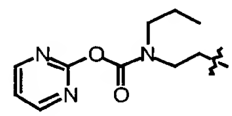
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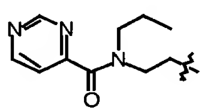
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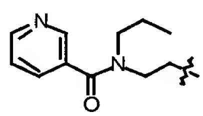
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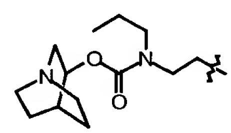
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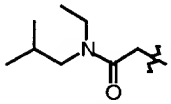
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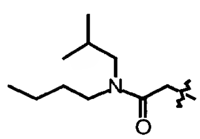
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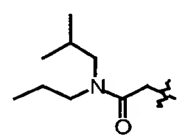
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Table 1 cont.

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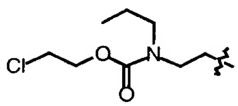

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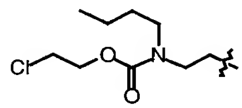

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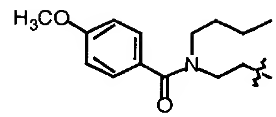

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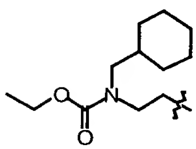

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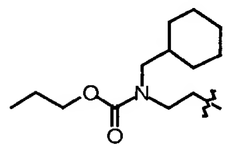

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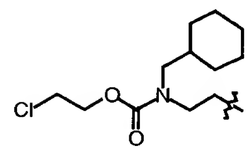

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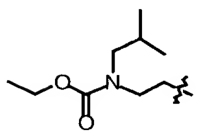

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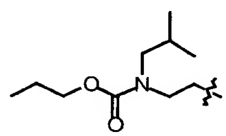

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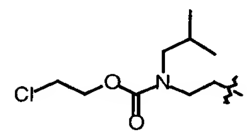

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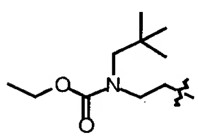

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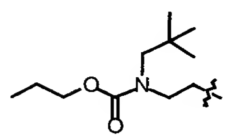

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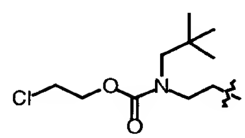

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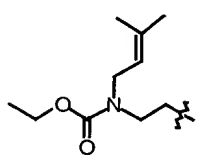

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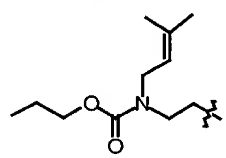

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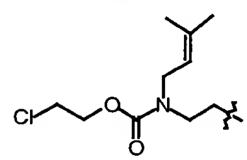

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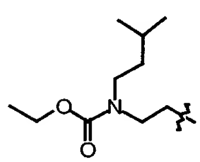

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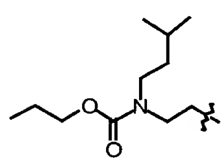

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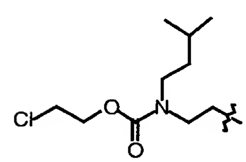

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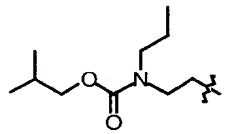
Table 1 cont.

R **R** **R**



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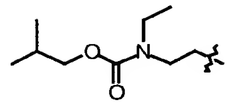

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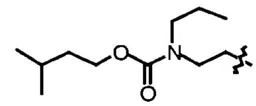

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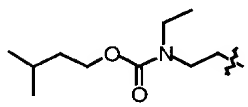

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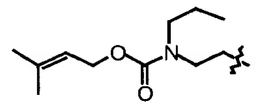

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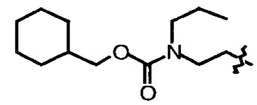

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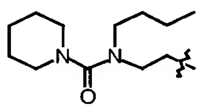

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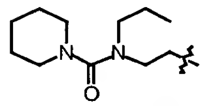

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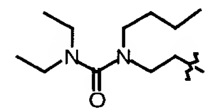

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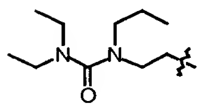

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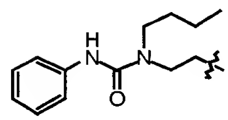

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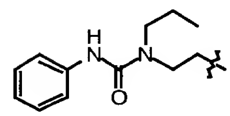

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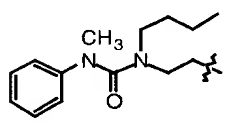

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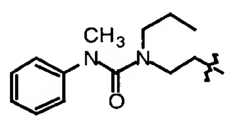

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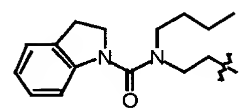

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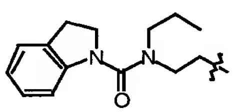

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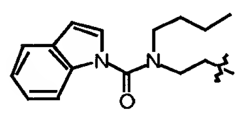

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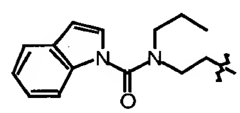

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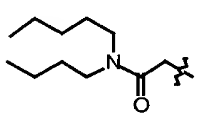

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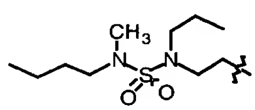

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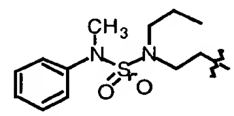

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Table 1 cont.

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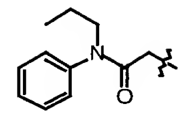

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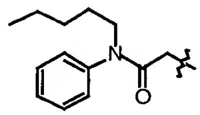

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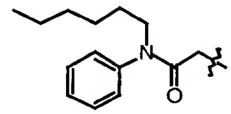

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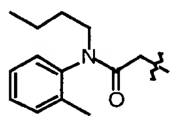

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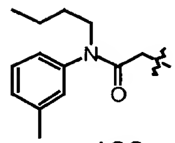

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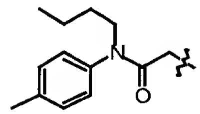

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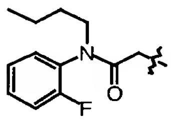

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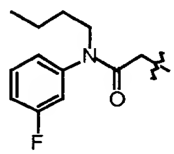

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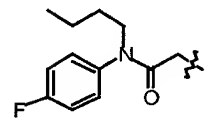

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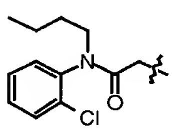

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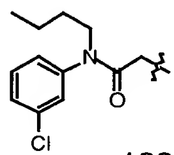

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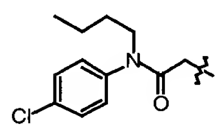

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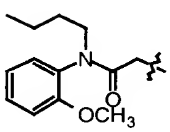

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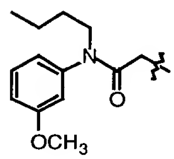

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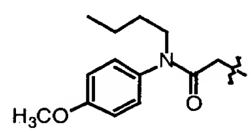

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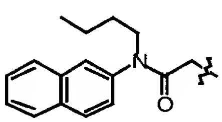

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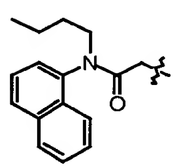

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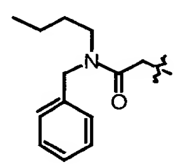

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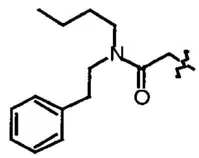
Table 1 cont.

R **R** **R**



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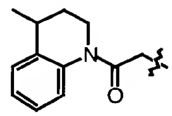

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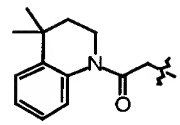

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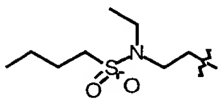

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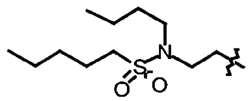

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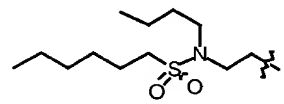

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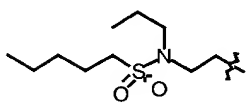

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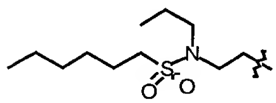

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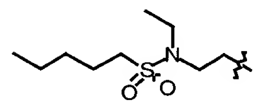

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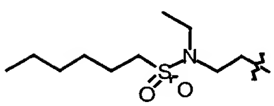

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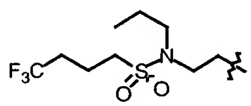

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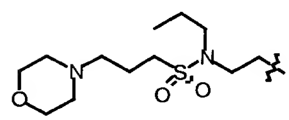

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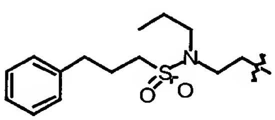

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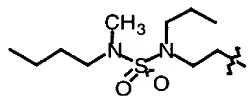

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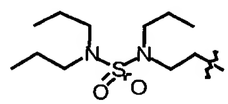

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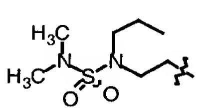

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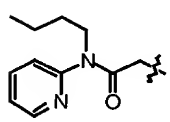

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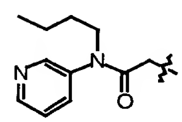

153.

Table 1 cont.

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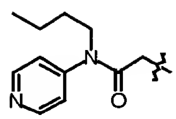

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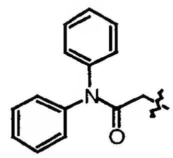

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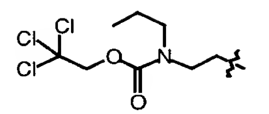

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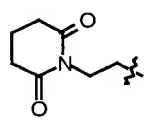

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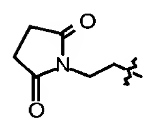

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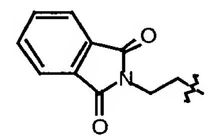

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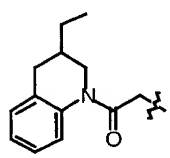

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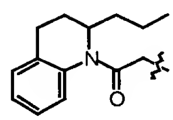

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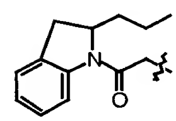

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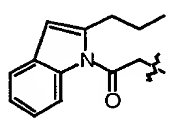

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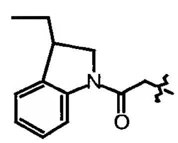

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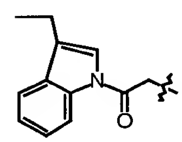

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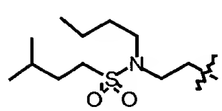

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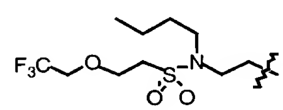

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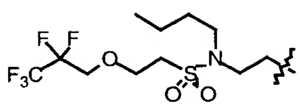

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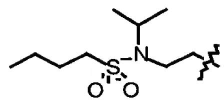

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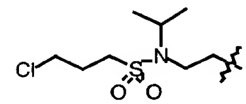

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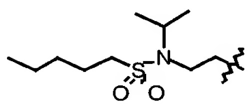

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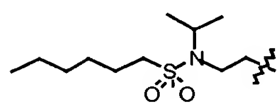

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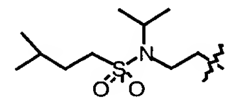

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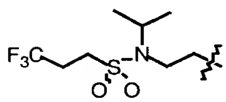

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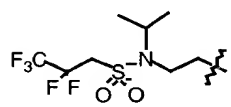

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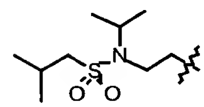

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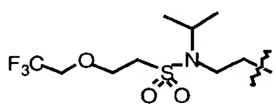

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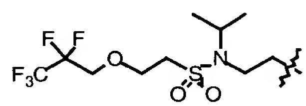

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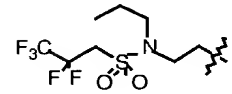

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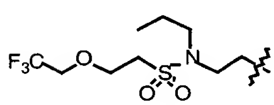

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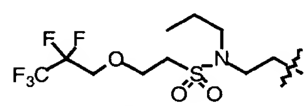

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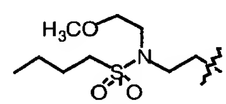

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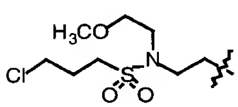

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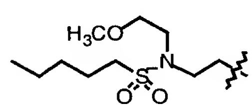

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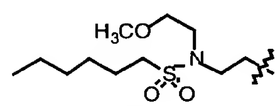

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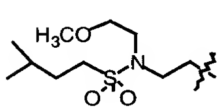

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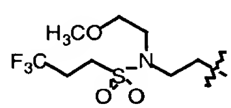

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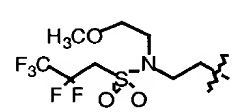

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Table 1 cont.

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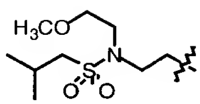
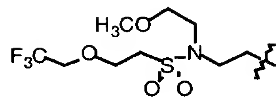
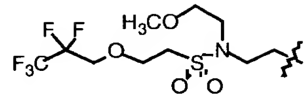
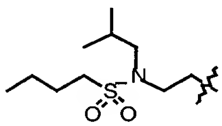
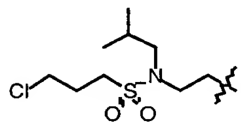
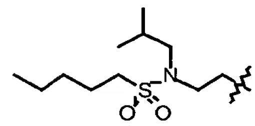
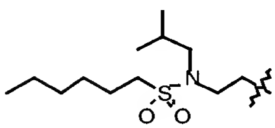
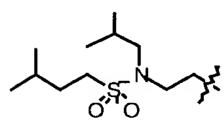
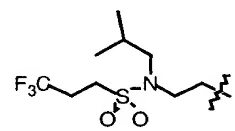
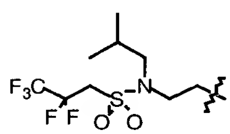
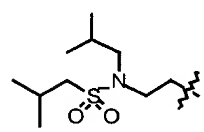
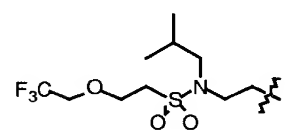
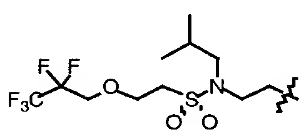
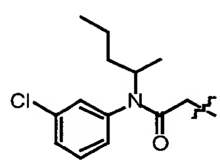
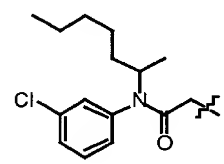
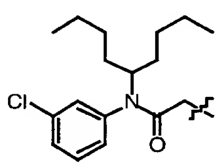
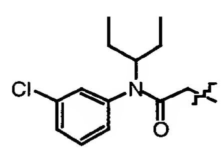
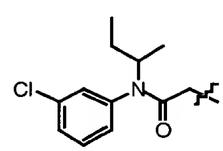
 190.	 191.	 192.
 193.	 194.	 195.
 196.	 197.	 198.
 199.	 200.	 201.
 202.	 203.	 204.
 205.	 206.	 207.

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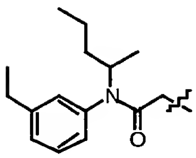

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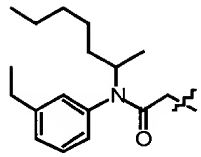

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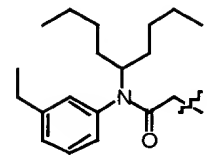

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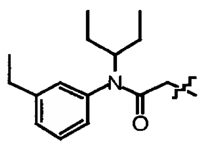

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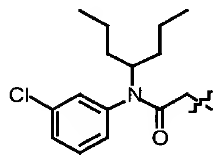

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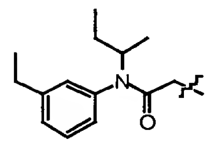

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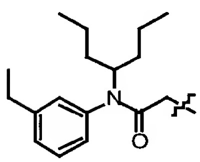

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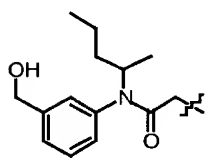

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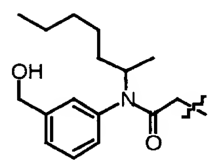

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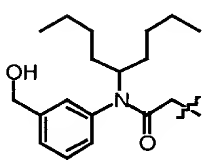

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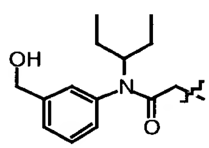

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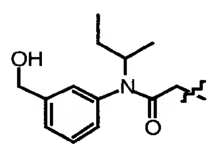

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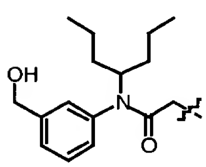

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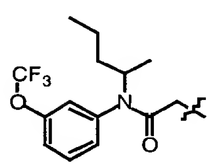

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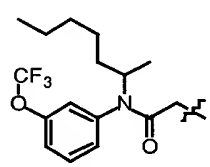

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Table 1 cont.

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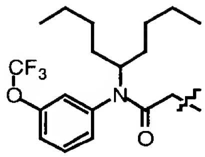

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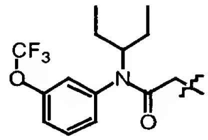

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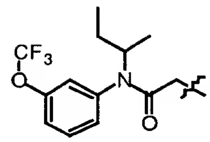

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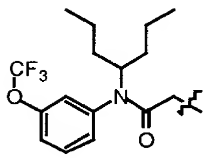

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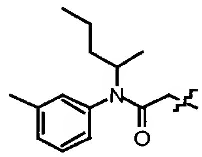

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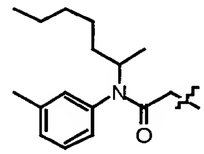

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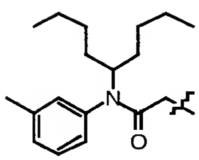

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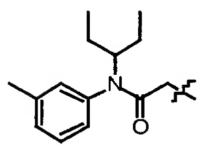

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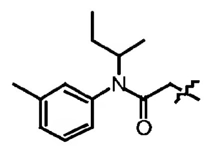

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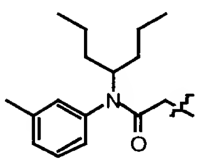

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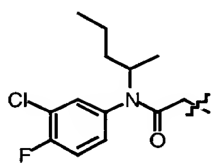

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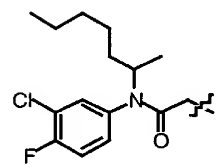

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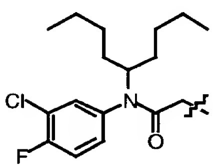

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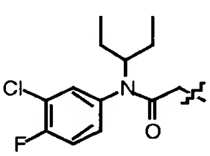

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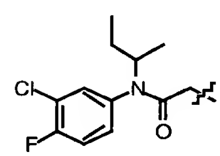

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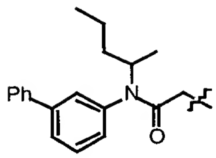
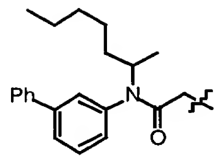
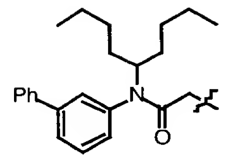
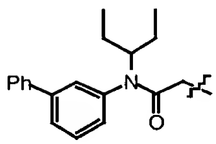
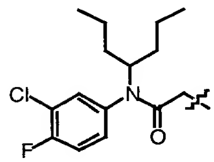
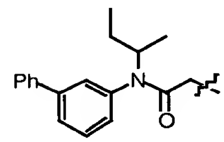
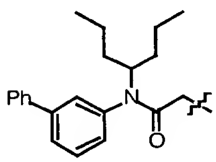
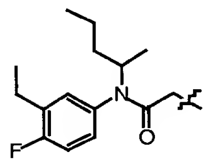
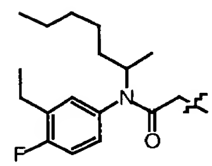
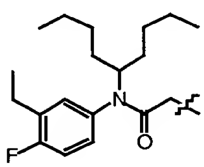
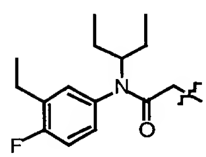
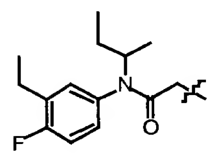
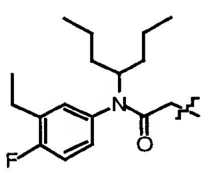
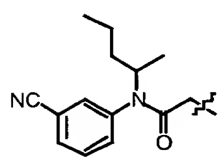
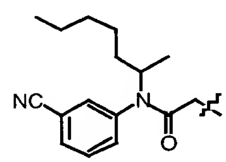
 238.	 239.	 240.
 241.	 242.	 243.
 244.	 245.	 246.
 247.	 248.	 249.
 250.	 251.	 252.

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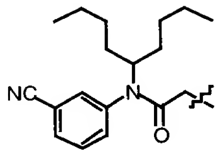
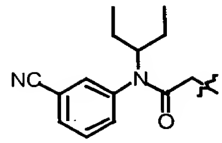
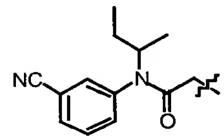
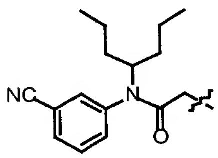
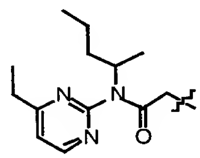
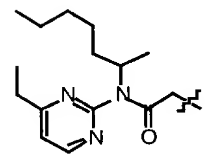
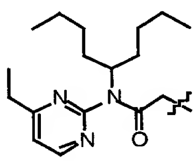
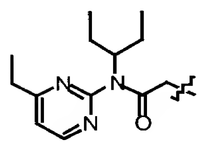
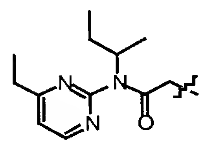
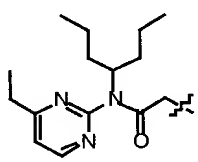
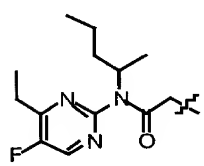
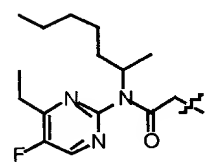
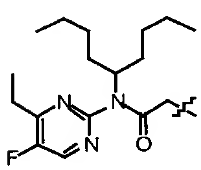
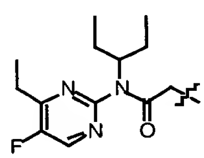
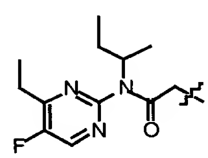
 253.	 254.	 255.
 256.	 257.	 258.
 259.	 260.	 261.
 262.	 263.	 264.
 265.	 266.	 267.

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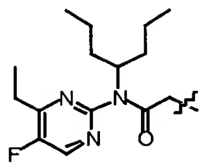

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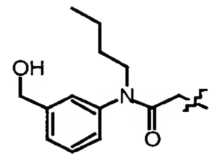

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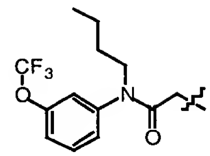

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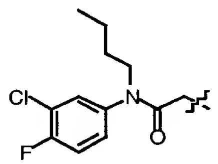

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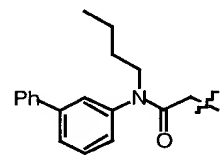

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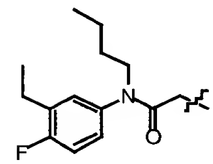

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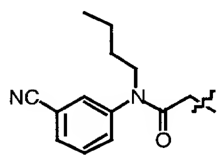

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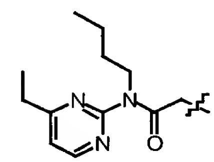

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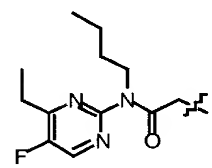

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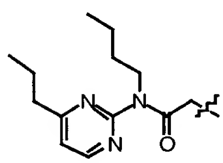

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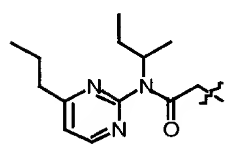

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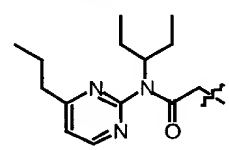

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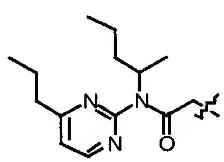

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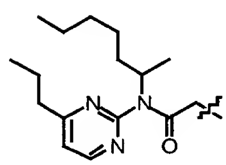

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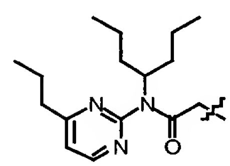

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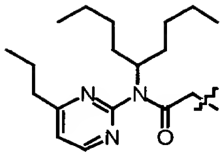
Table 1 cont.

R **R** **R**



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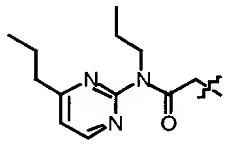

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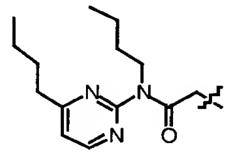

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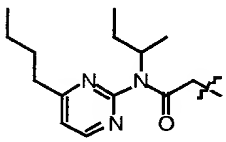

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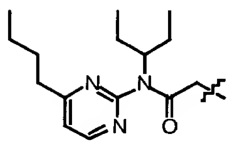

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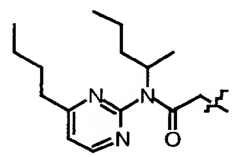

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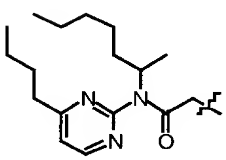

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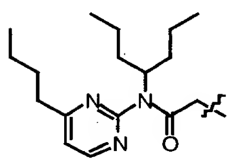

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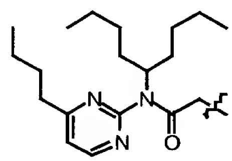

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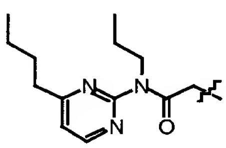

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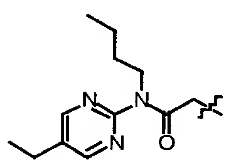

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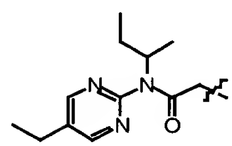

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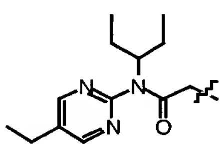

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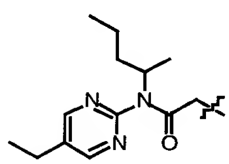

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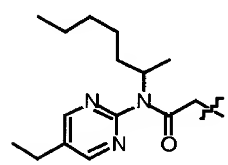

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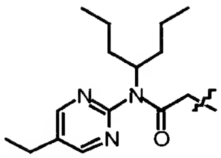
Table 1 cont.

R **R** **R**



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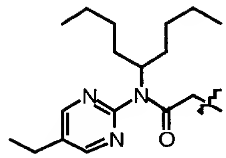

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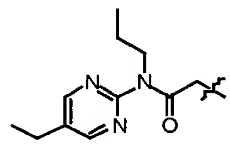

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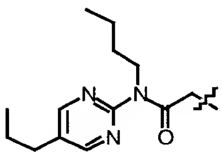

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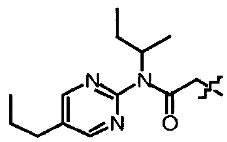

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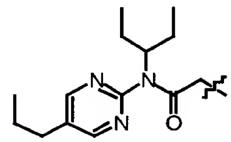

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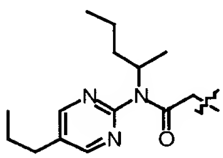

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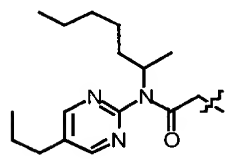

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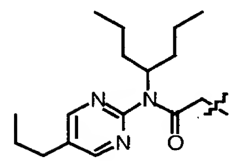

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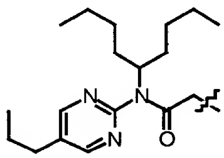

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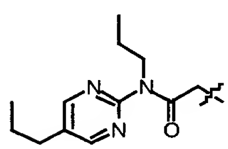

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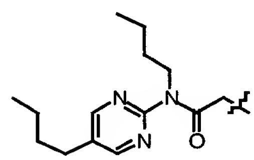

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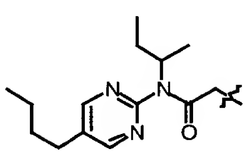

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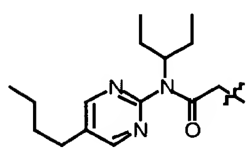

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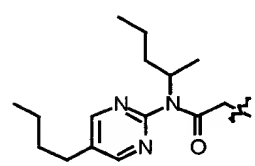

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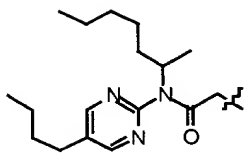

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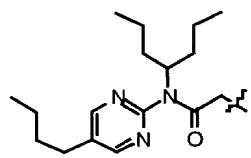

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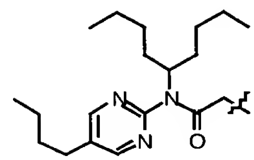

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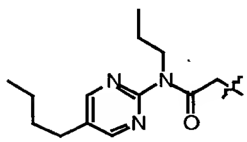

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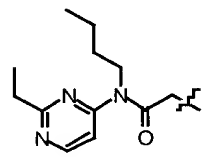

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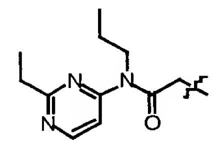

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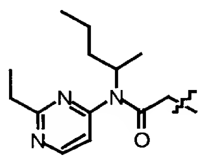

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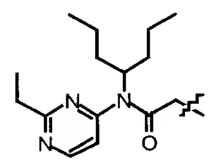

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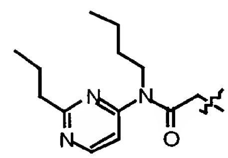

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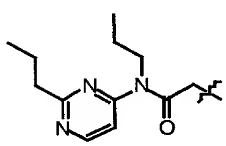

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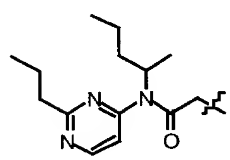

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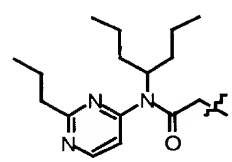

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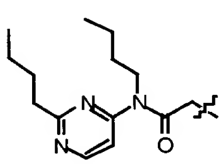

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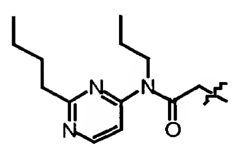

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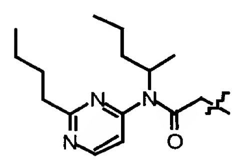

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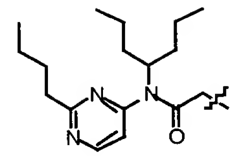
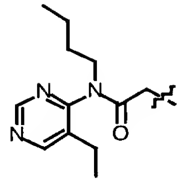
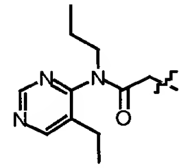
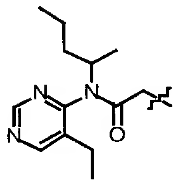
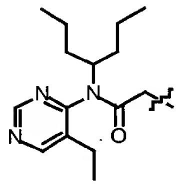
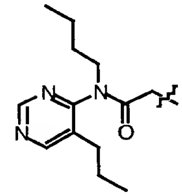
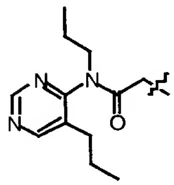
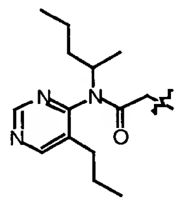
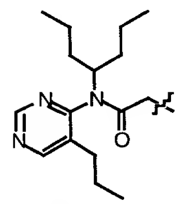
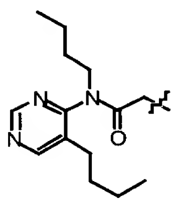
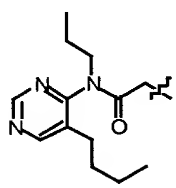
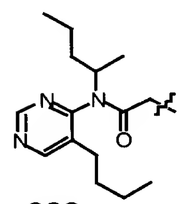
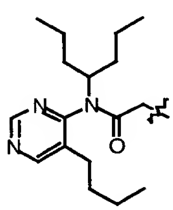
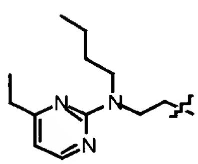
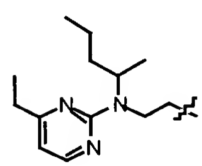
 328.	 329.	 330.
 331.	 332.	 333.
 334.	 335.	 336.
 337.	 338.	 339.
 340.	 341.	 342.

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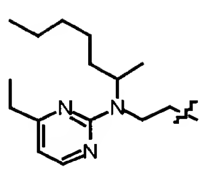

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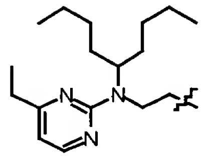

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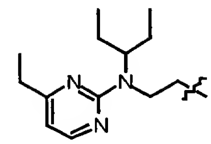

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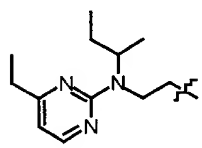

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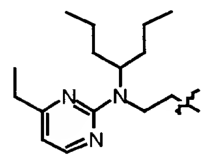

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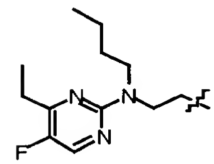

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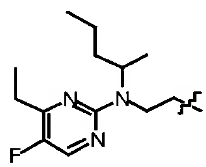

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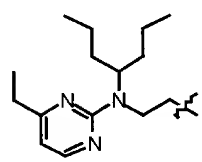

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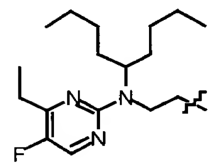

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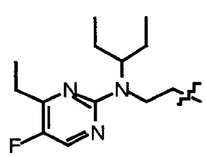

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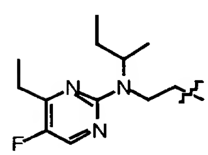

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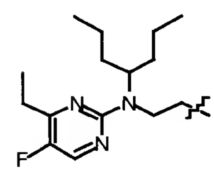

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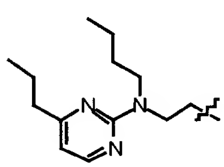

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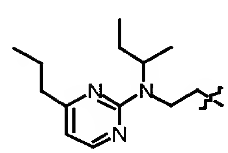

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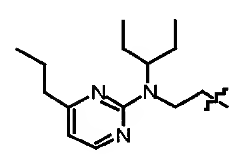

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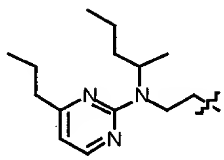

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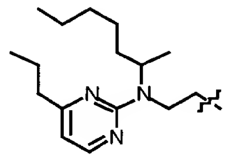

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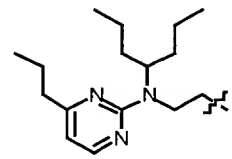

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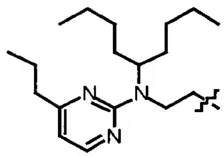

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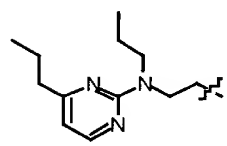

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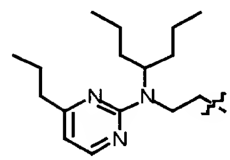

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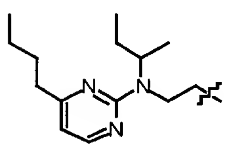

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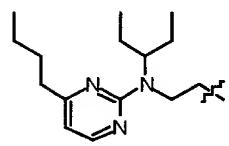

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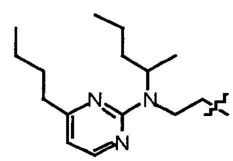

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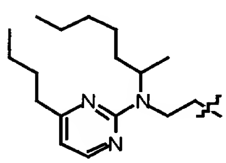

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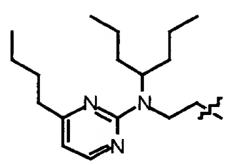

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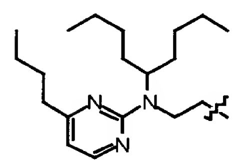

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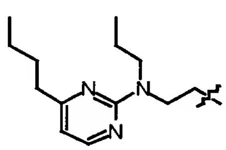

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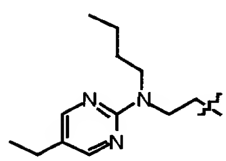

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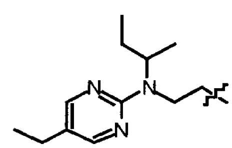

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Table 1 cont.

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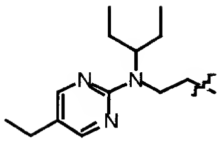

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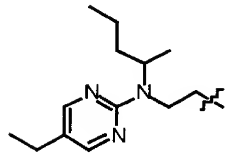

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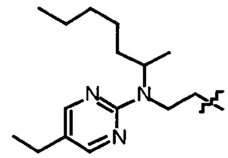

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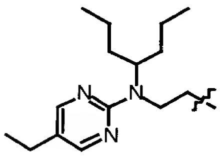

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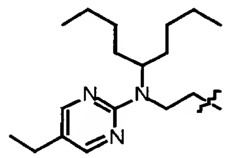

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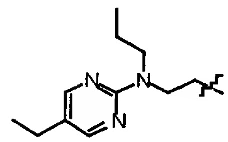

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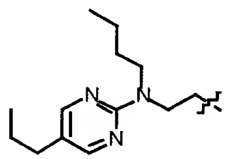

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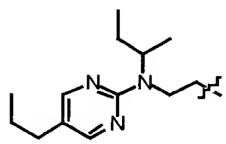

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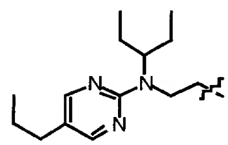

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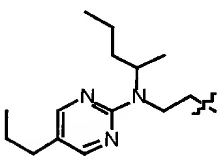

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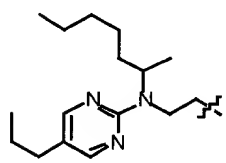

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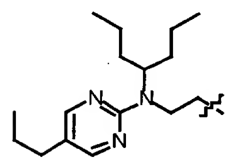

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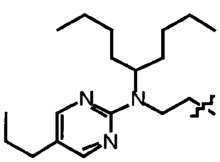

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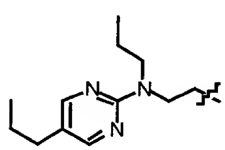

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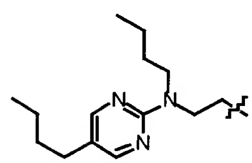

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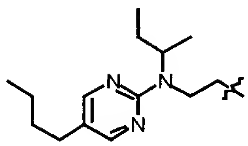
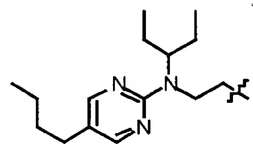
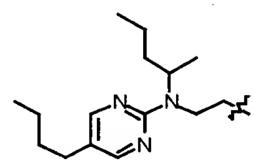
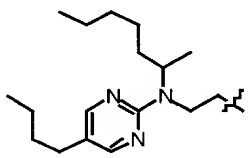
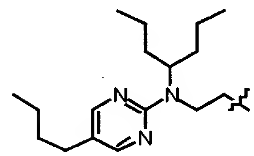
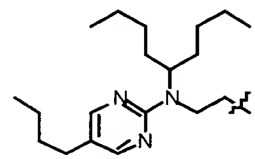
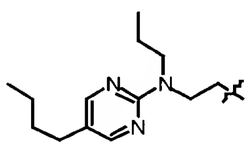
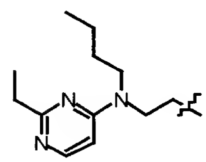
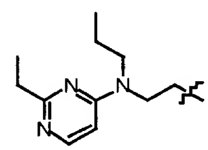
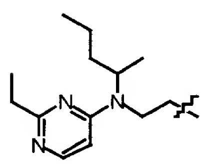
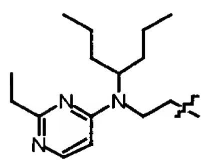
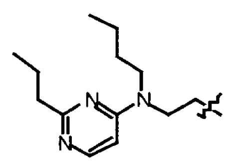
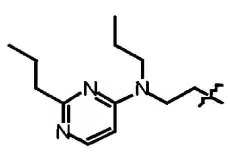
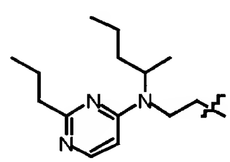
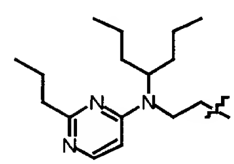
 388.	 389.	 390.
 391.	 392.	 393.
 394.	 395.	 396.
 397.	 398.	 399.
 400.	 401.	 402.

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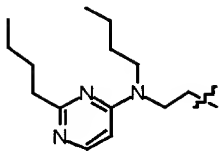
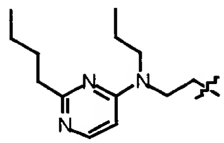
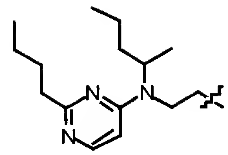
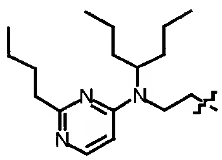
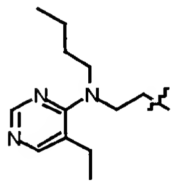
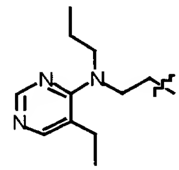
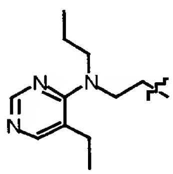
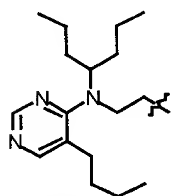
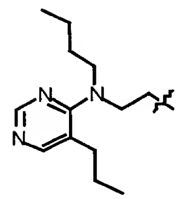
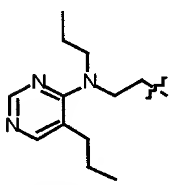
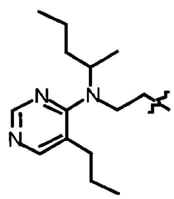
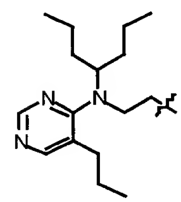
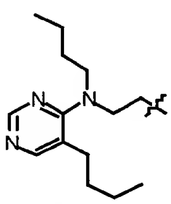
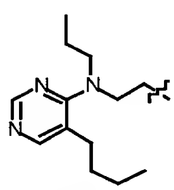
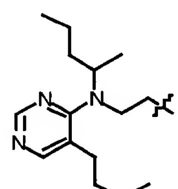
 403.	 404.	 405.
 406.	 407.	 408.
 409.	 410.	 411.
 412.	 413.	 414.
 415.	 416.	 417.

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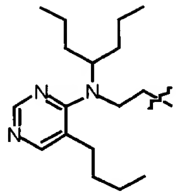

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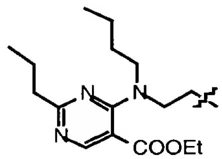

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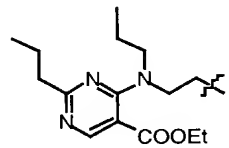

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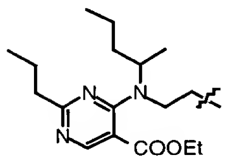

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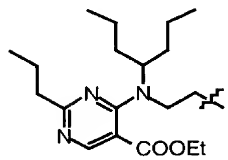

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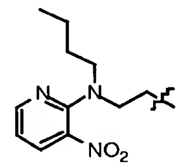

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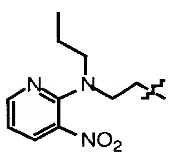

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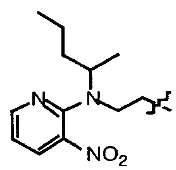

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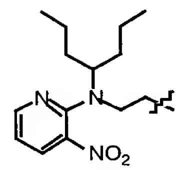

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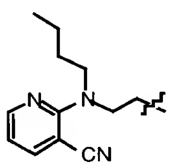

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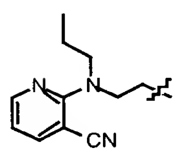

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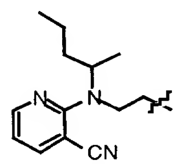

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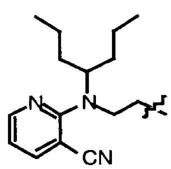

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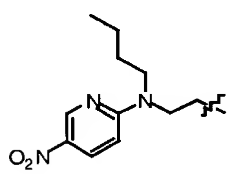

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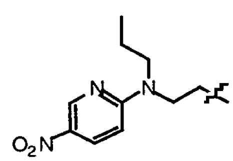

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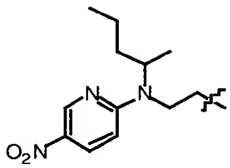

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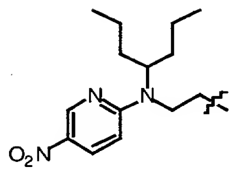

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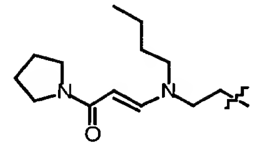

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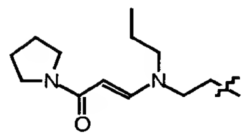

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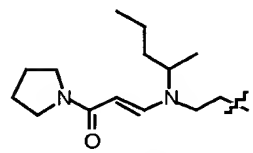

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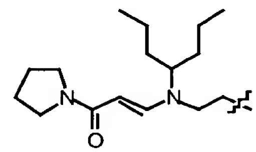

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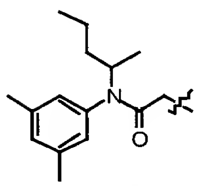

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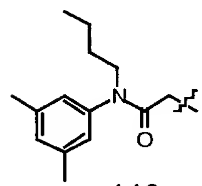

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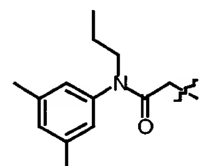

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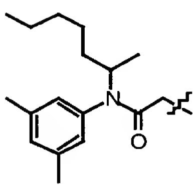

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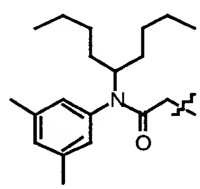

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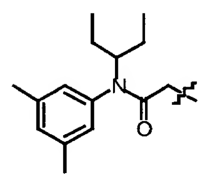

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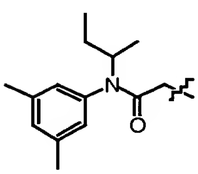

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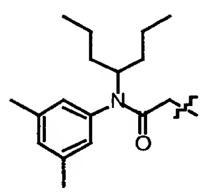

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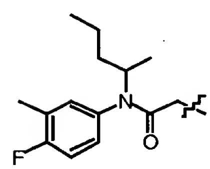

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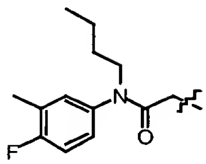

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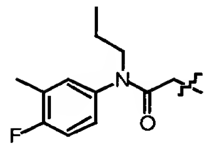

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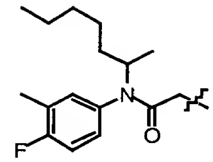

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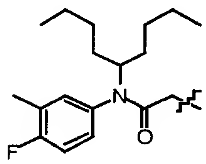

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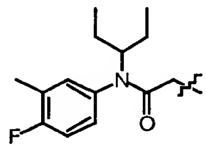

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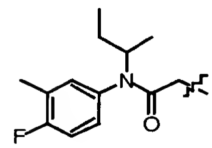

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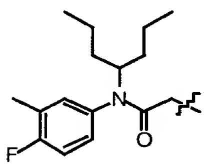

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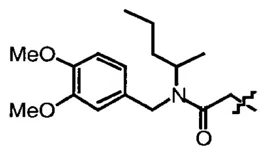

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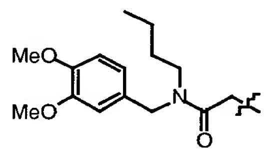

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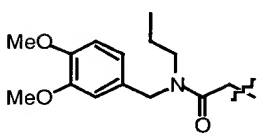

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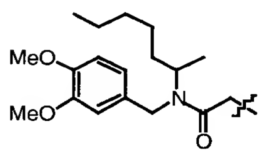

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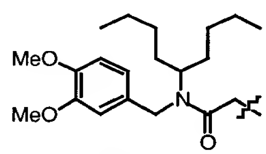

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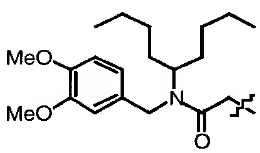

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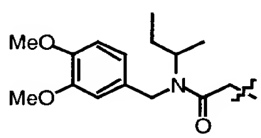

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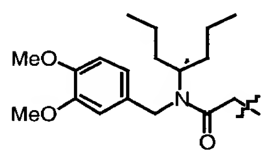

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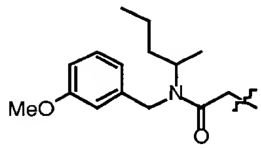
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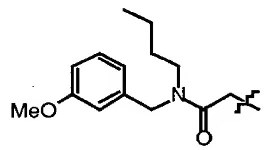
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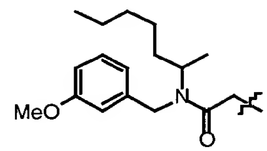
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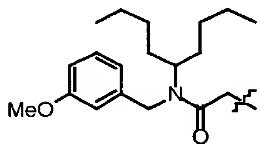
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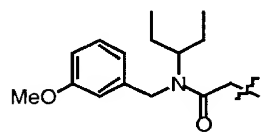
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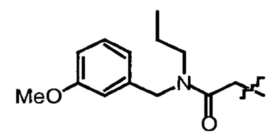
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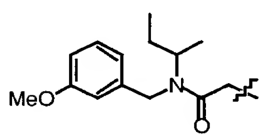
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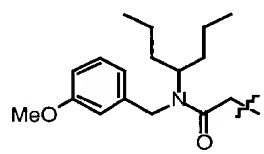
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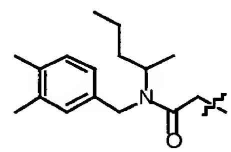
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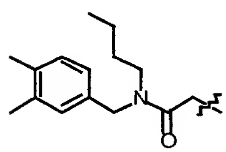
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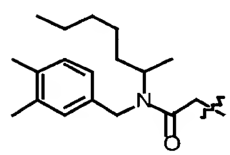
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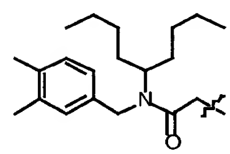
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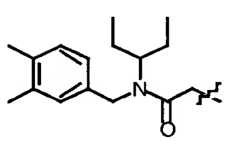
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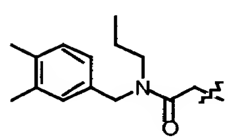
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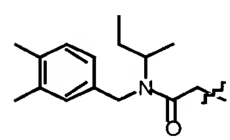
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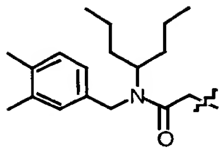

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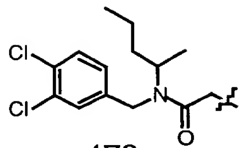

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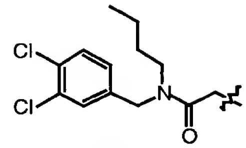

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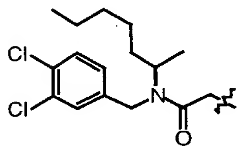

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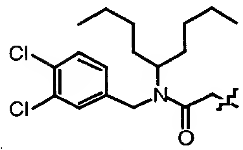

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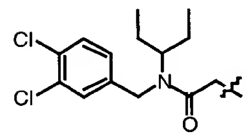

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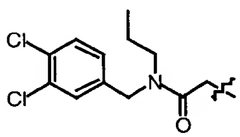

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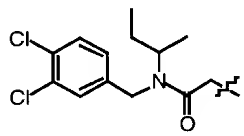

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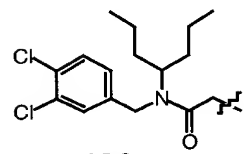

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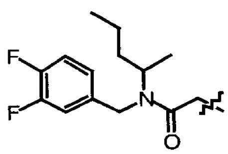

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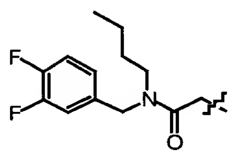

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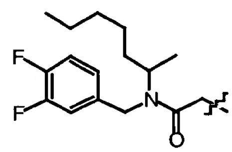

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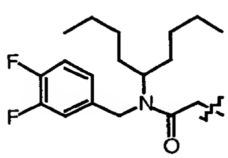

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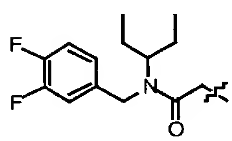

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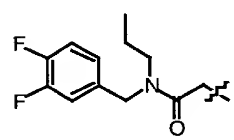

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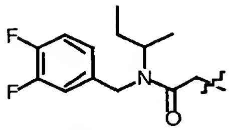
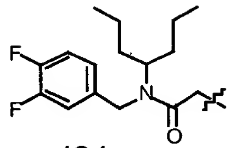
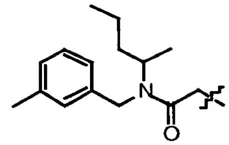
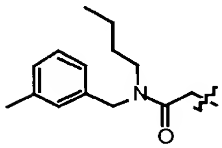
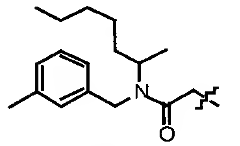
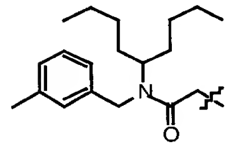
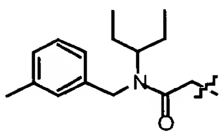
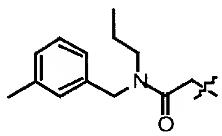
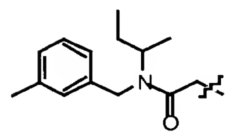
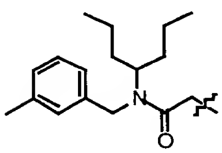
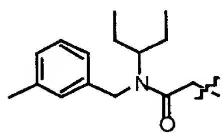
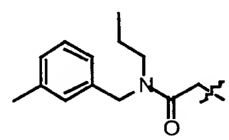
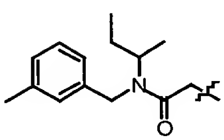
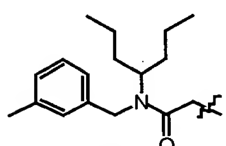
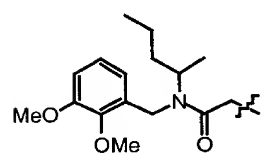
 493.	 494.	 495.
 496.	 497.	 498.
 499.	 500.	 501.
 502.	 503.	 504.
 505.	 506.	 507.

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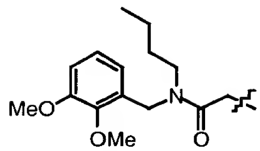

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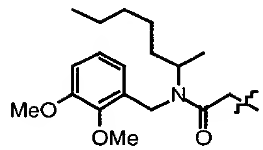

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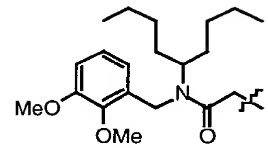

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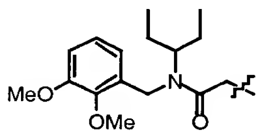

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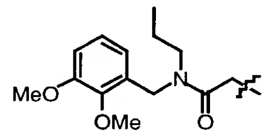

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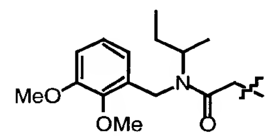

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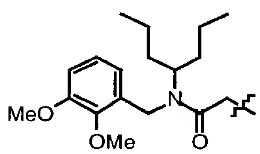

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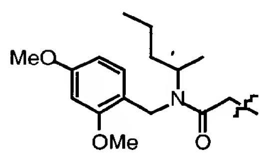

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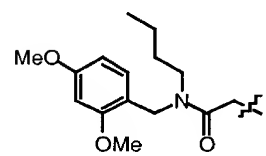

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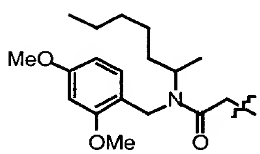

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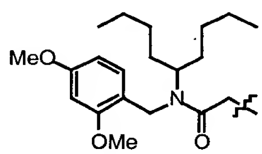

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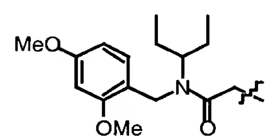

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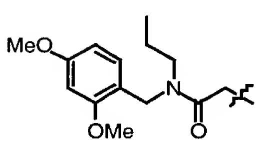

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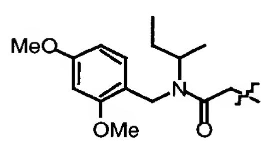

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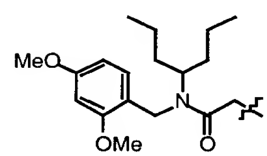

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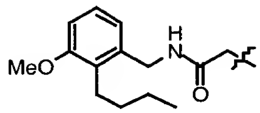
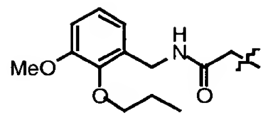
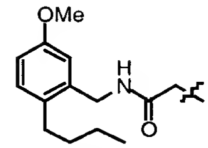
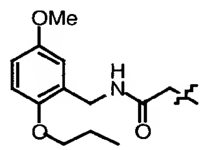
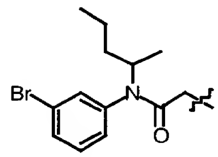
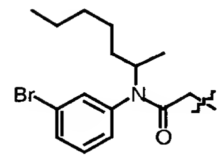
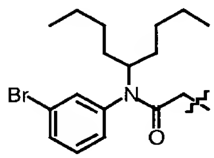
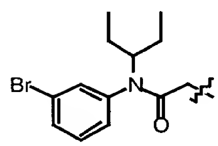
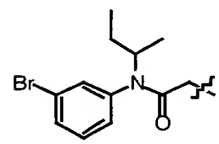
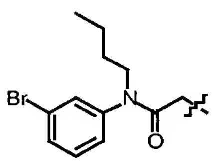
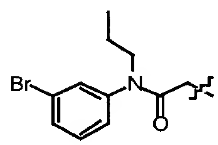
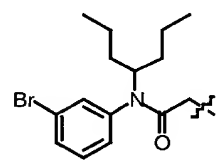
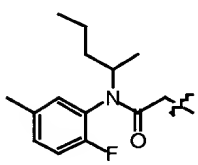
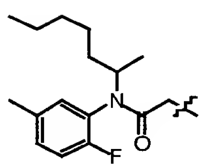
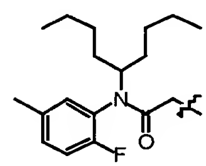
 523.	 524.	 525.
 526.	 527.	 528.
 529.	 530.	 531.
 532.	 533.	 534.
 535.	 536.	 537.

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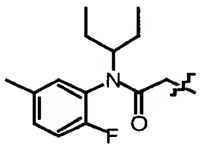
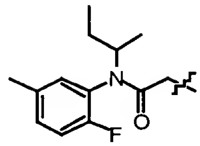
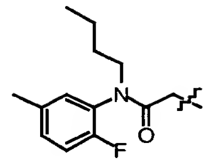
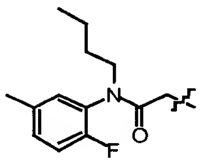
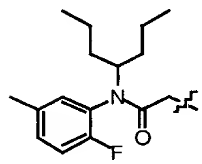
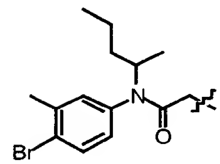
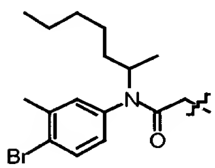
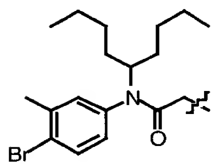
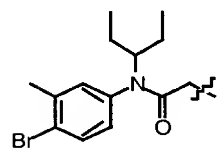
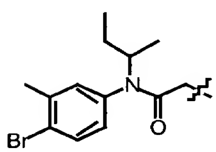
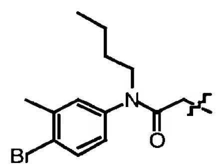
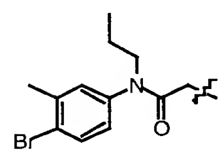
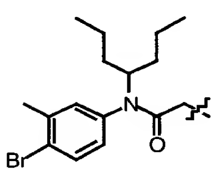
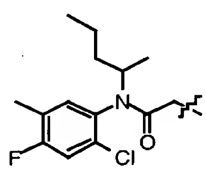
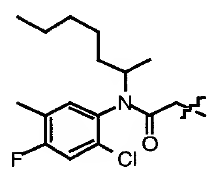
 538.	 539.	 540.
 540.	 542.	 543.
 544.	 545.	 546.
 547.	 548.	 549.
 550.	 551.	 552.

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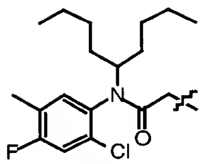
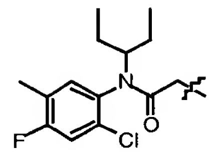
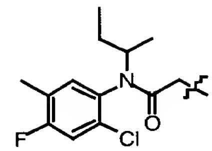
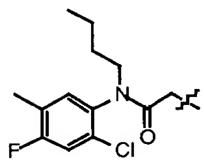
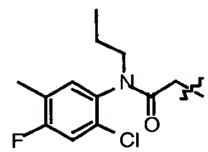
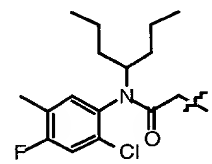
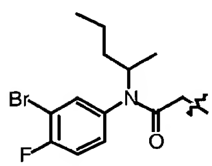
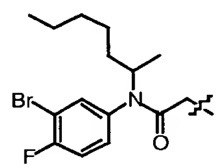
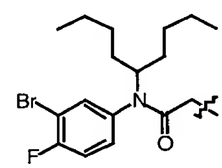
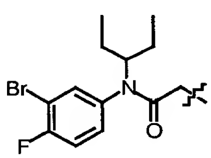
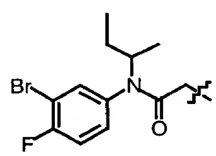
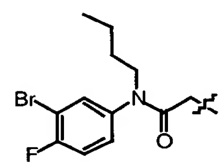
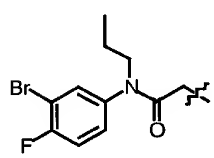
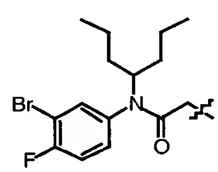
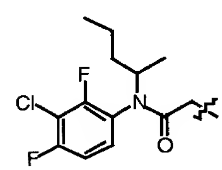
 553.	 554.	 555.
 556.	 557.	 558.
 559.	 560.	 561.
 562.	 563.	 564.
 565.	 566.	 567.

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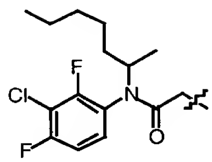

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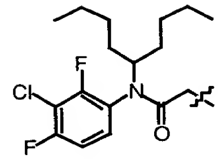

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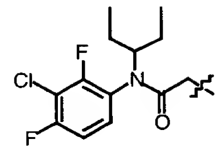

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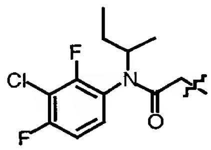

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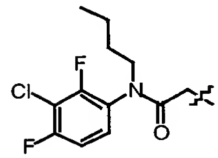

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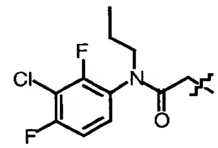

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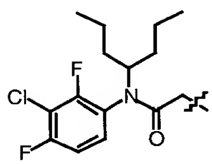

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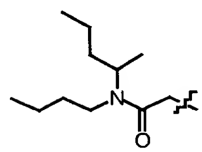

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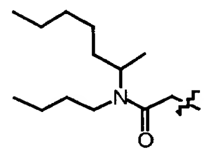

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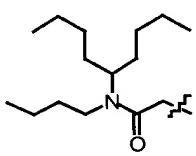

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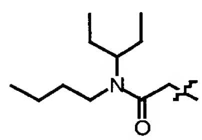

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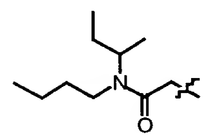

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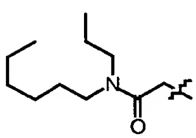

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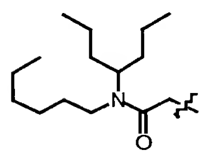

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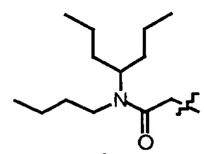

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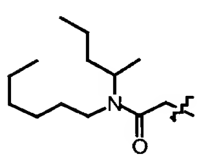

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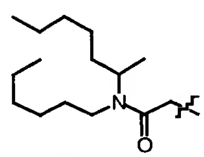

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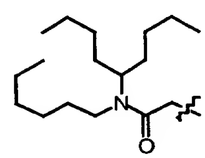

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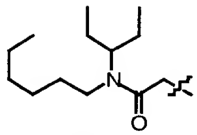
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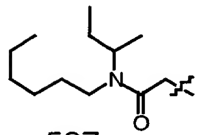
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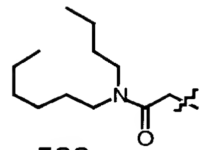
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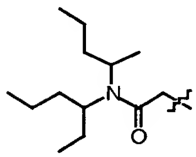
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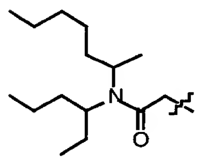
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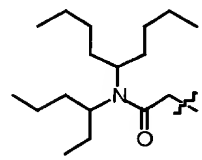
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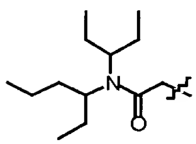
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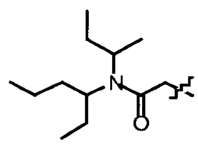
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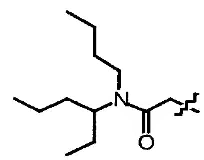
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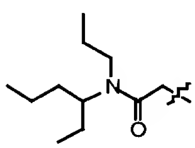
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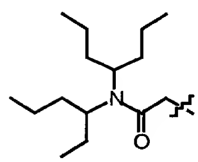
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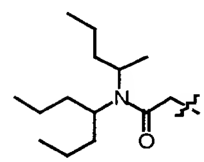
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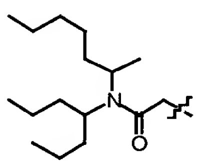
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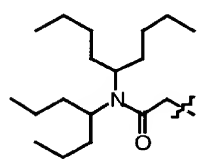
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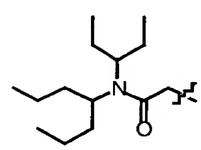
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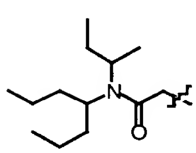
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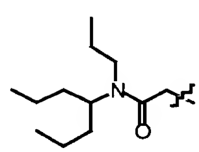
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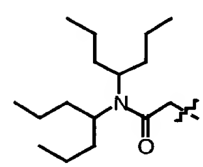
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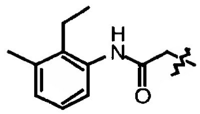
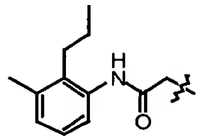
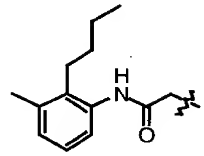
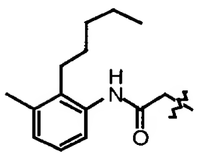
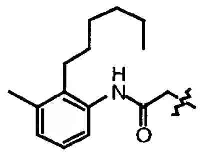
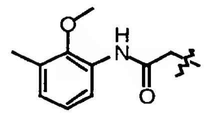
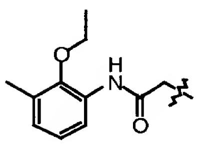
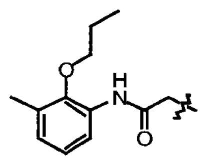
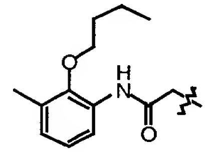
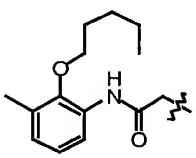
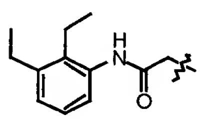
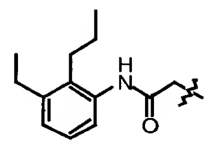
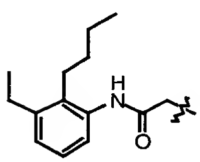
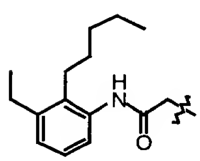
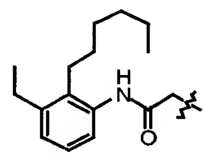
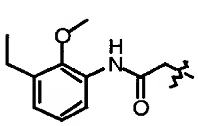
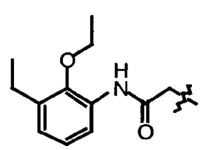
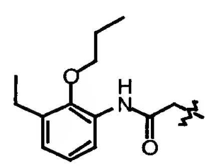
 604.	 605.	 606.
 607.	 608.	 609.
 610.	 611.	 612.
 613.	 614.	 615.
 616.	 617.	 618.
 619.	 620.	 621.

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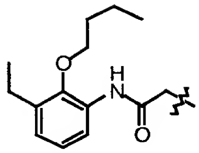

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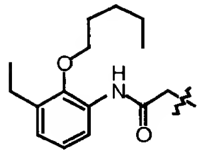

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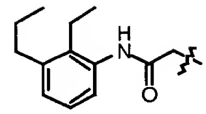

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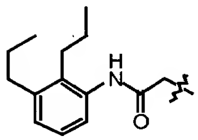

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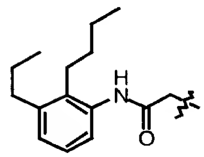

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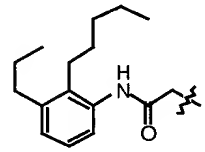

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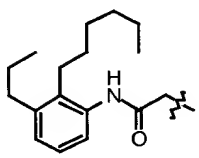

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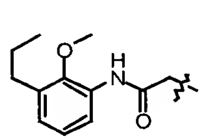

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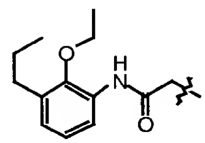

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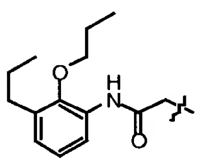

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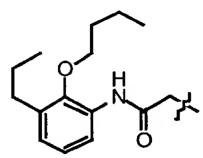

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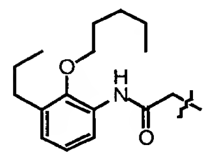

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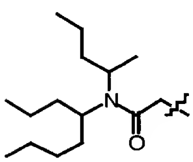

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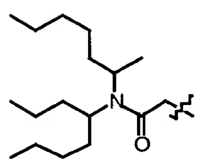

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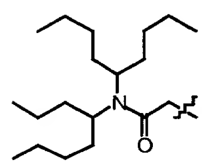

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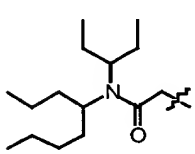

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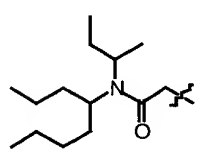

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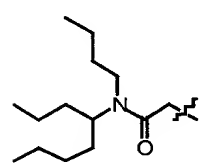

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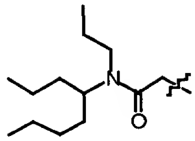
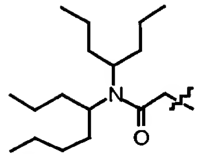
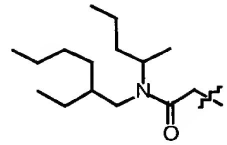
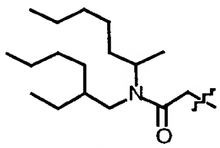
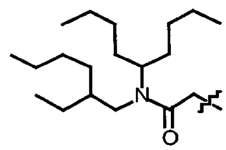
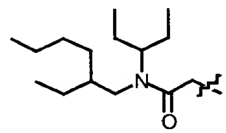
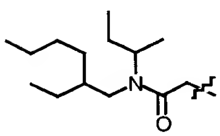
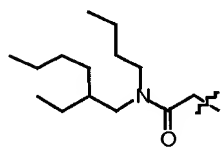
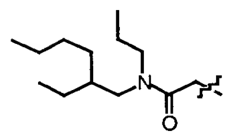
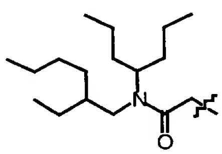
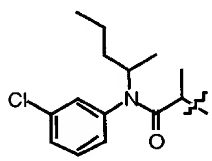
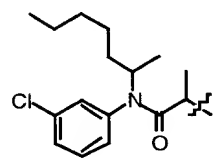
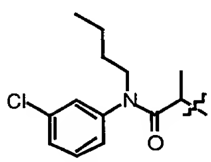
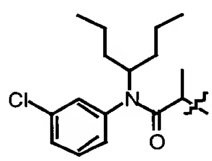
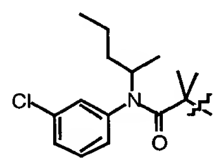
 640.	 641.	 642.
 643.	 644.	 645.
 646.	 647.	 648.
 649.	 650.	 651.
 652.	 653.	 654.

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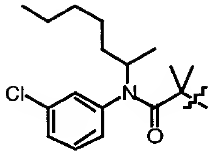

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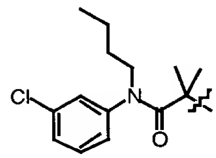

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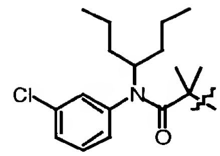

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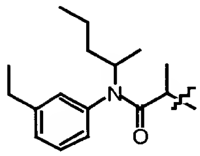

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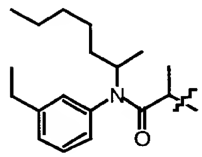

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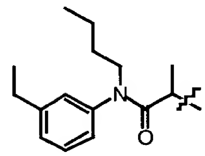

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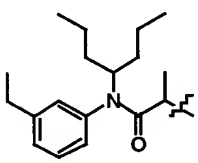

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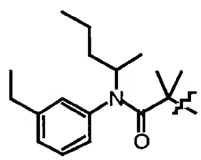

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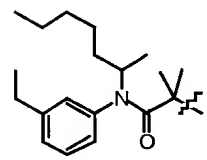

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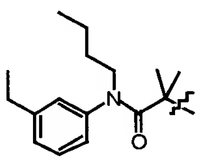

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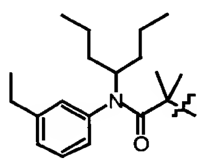

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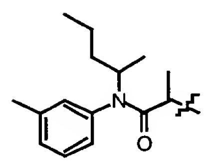

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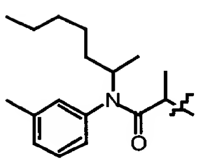

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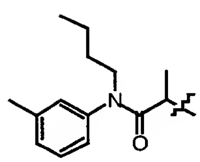

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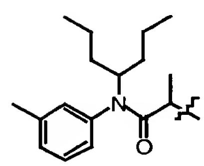

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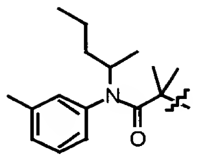
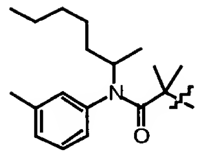
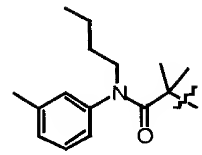
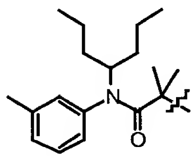
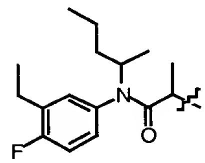
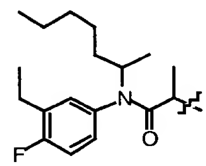
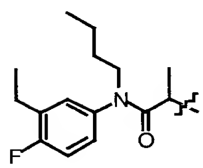
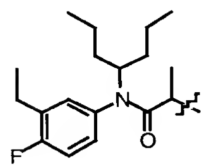
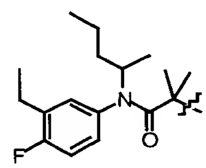
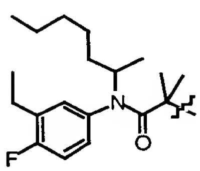
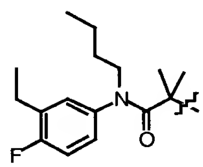
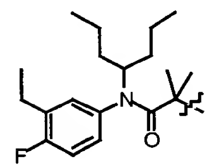
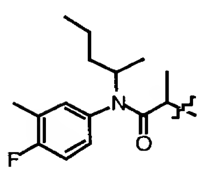
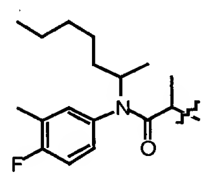
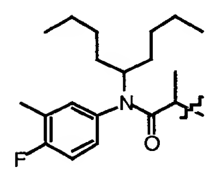
 670.	 671.	 672.
 673.	 674.	 675.
 676.	 677.	 678.
 679.	 680.	 681.
 682.	 683.	 684.

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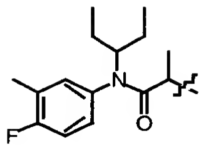
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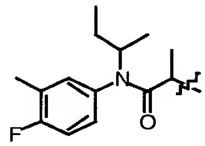
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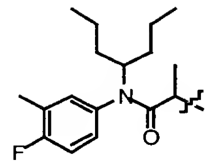
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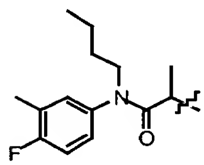
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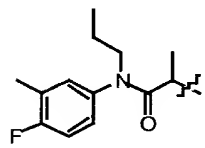
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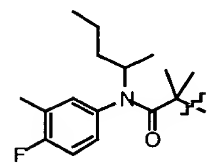
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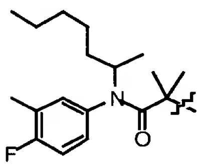
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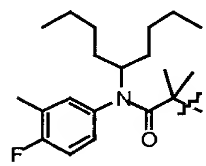
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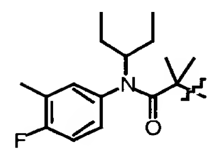
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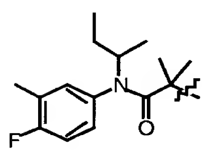
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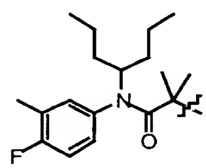
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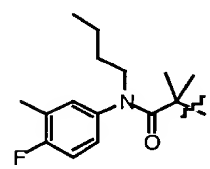
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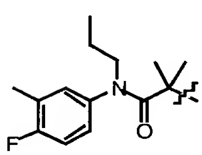
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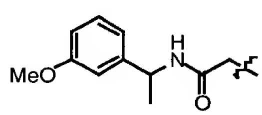

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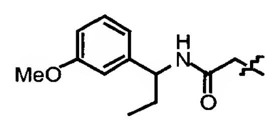

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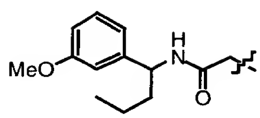
Table 1 cont.

R **R** **R**



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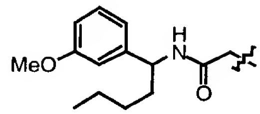

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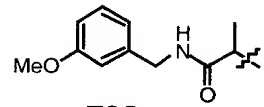

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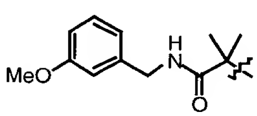

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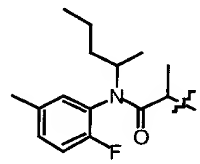

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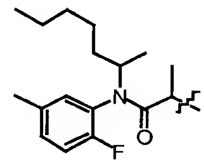

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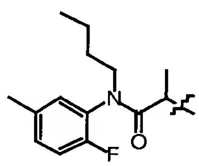

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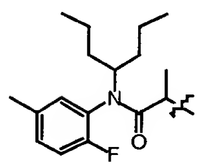

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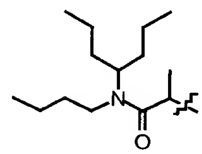

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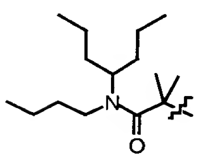

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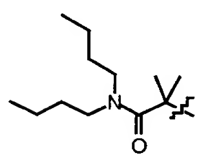

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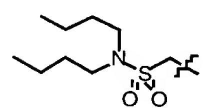

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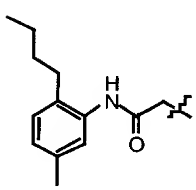

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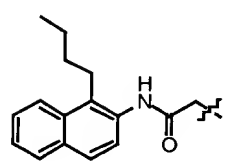

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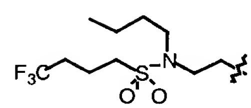

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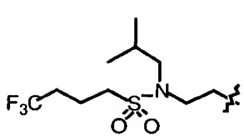
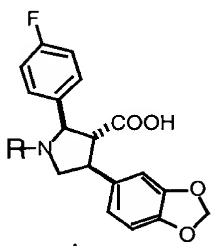


715.

Example 338

Using methods described in the above examples, compounds comprising a parent structure selected from those disclosed in Table 2A and an R substituent selected from those disclosed in Table 2B can be prepared.

Table 2A



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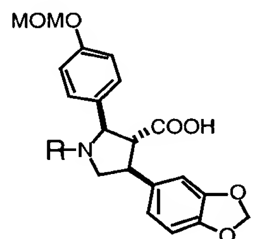

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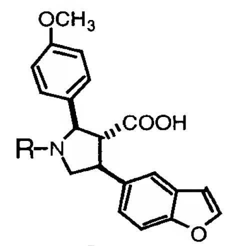

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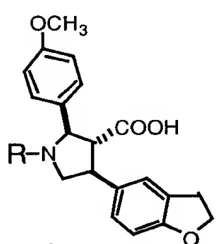

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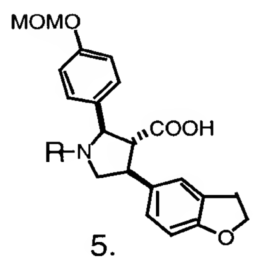

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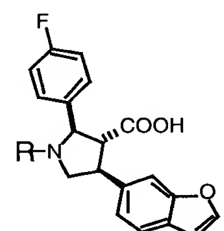

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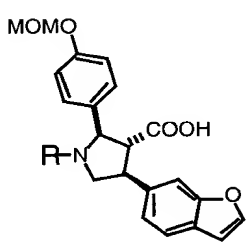

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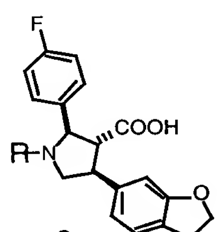

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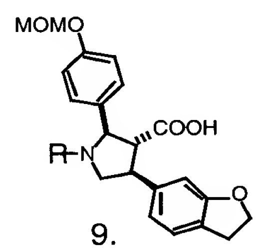

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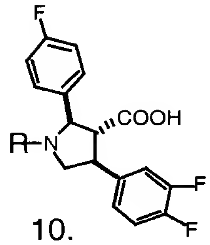

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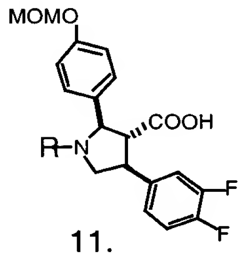

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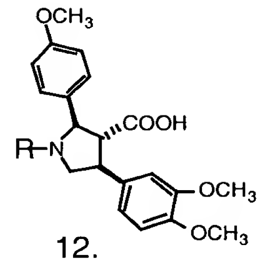

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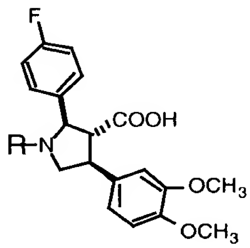

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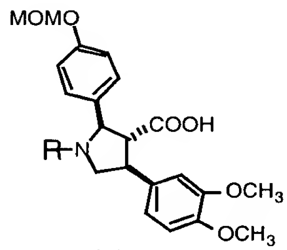

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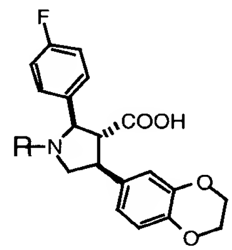

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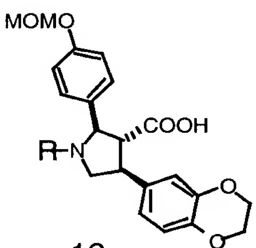

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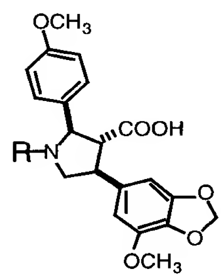

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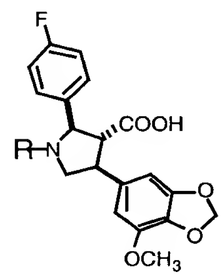

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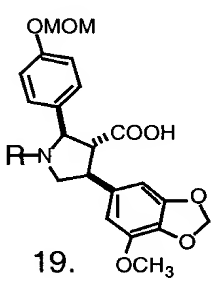

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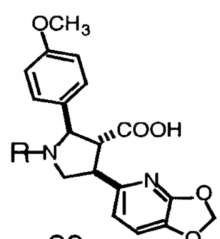

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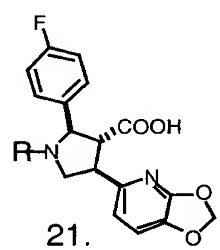

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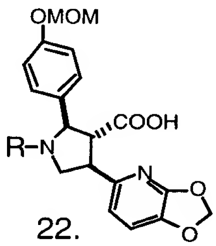

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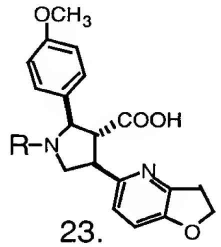

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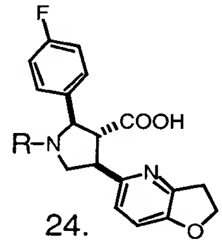

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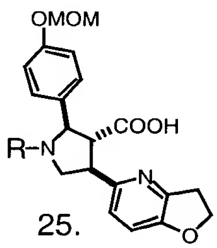

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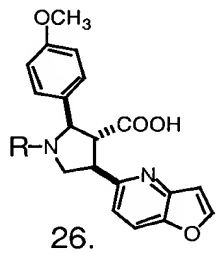

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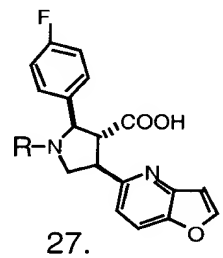

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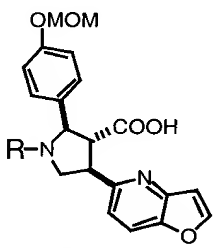

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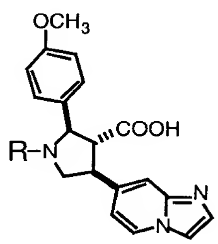

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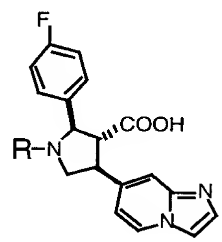

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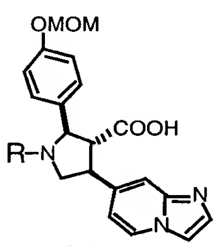

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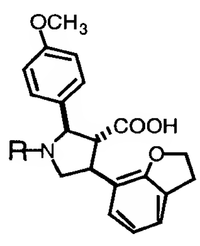

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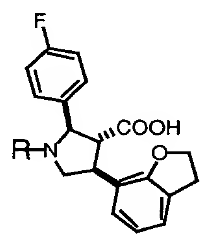

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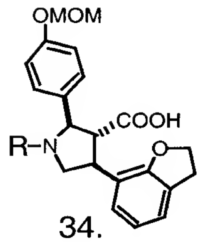

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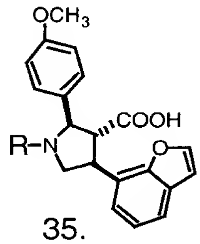

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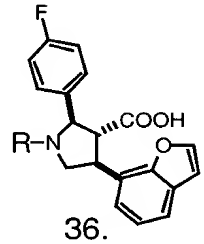

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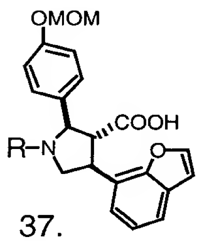

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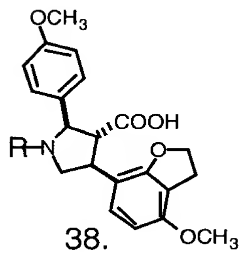

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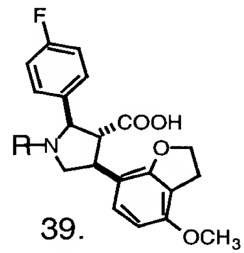

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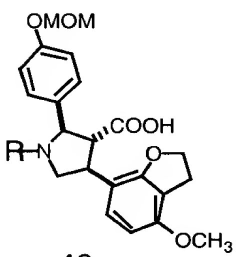

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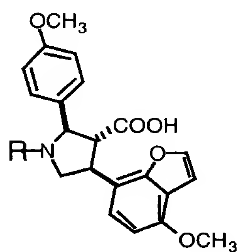

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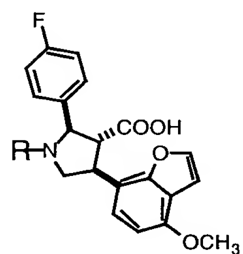

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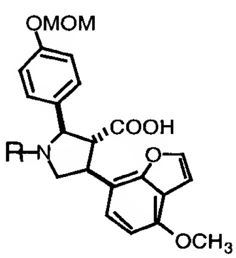

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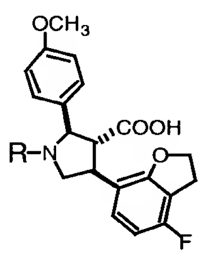

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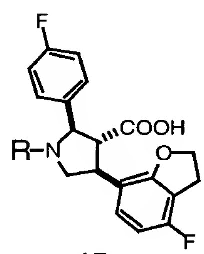

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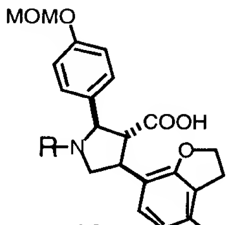

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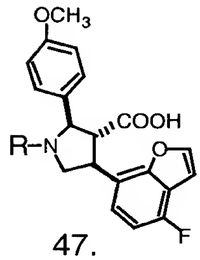

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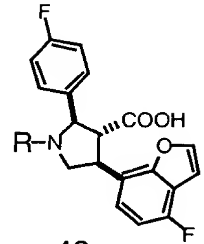

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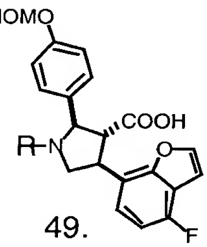

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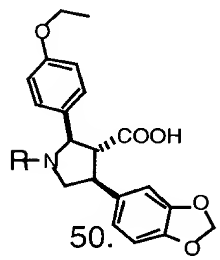

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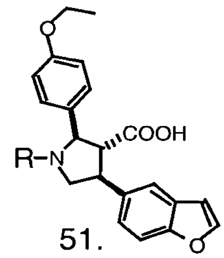

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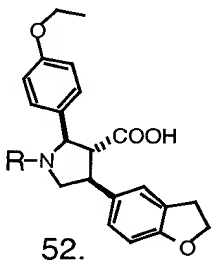

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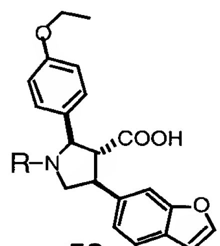

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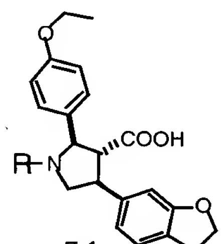

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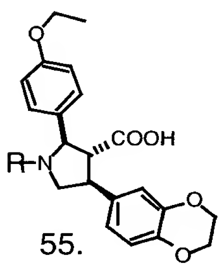

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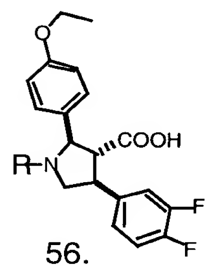

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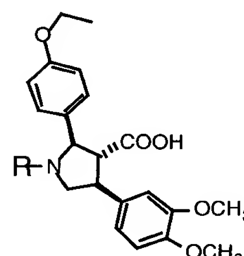

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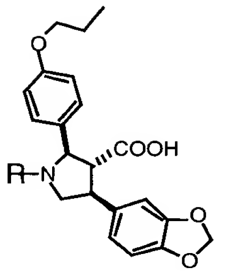

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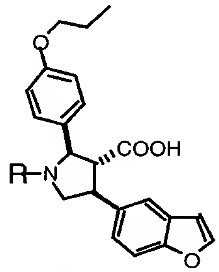

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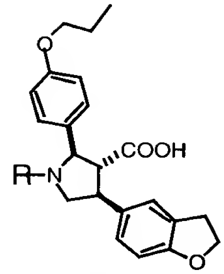

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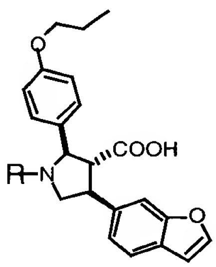

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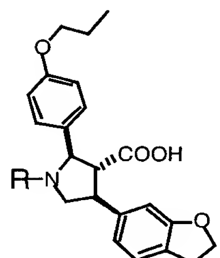

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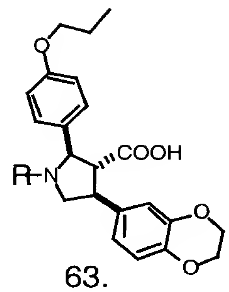

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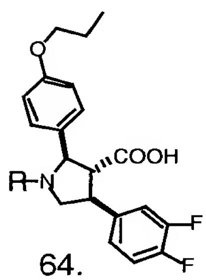

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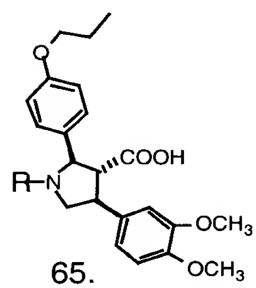

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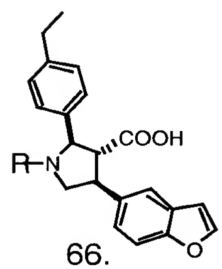

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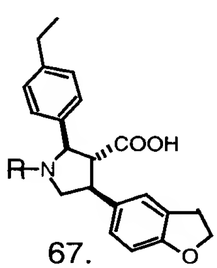

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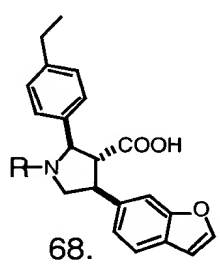

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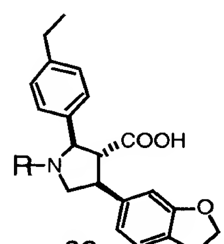

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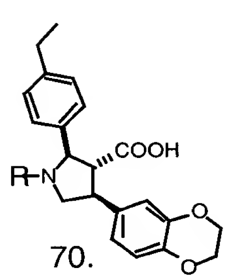
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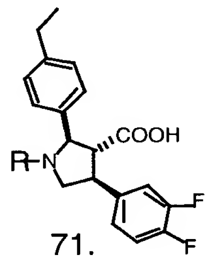
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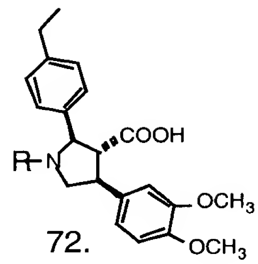
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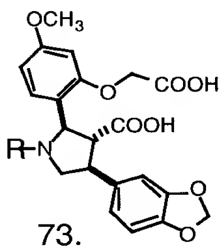
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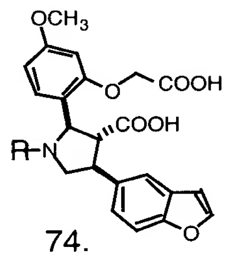
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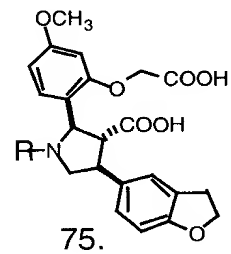
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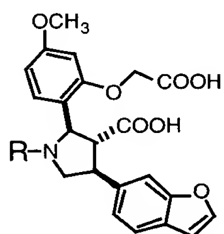
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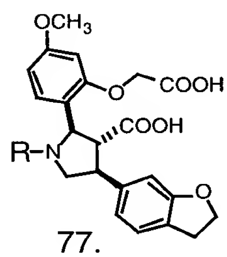
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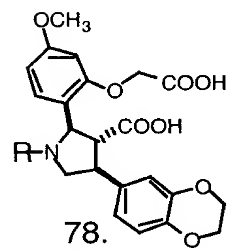
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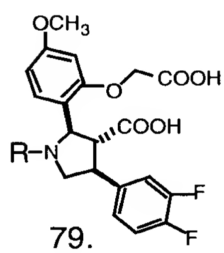
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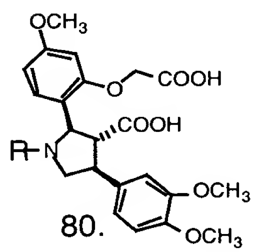
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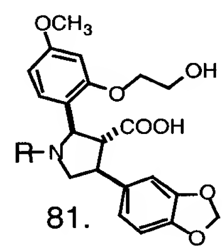
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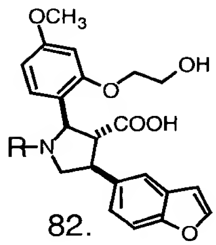

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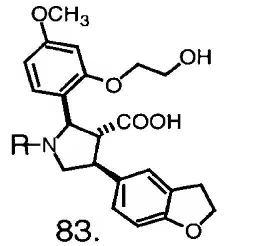

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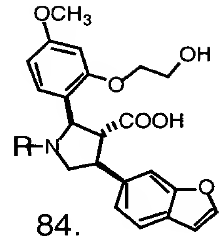

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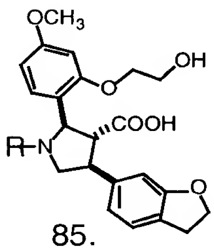

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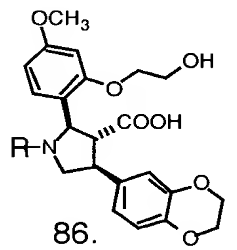

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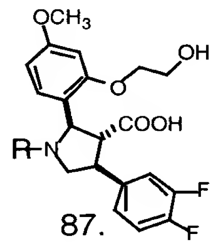

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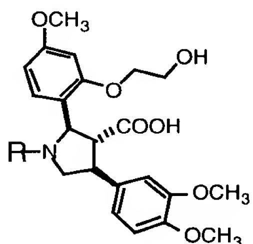

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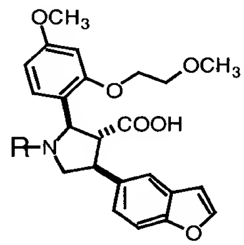

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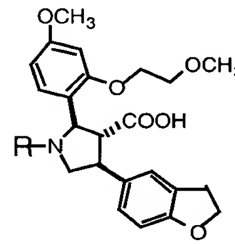

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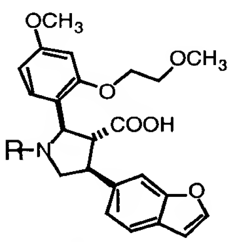

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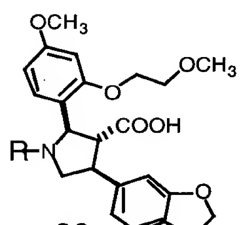

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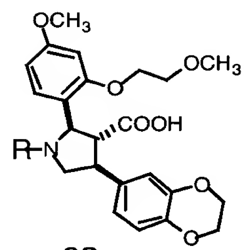

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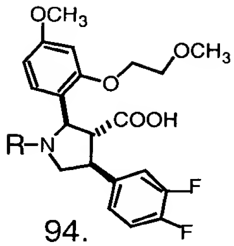
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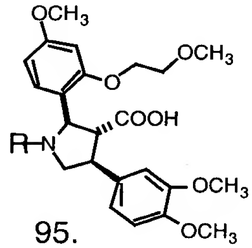
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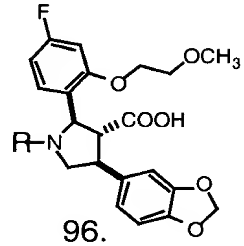
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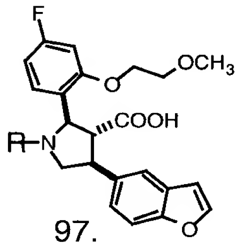
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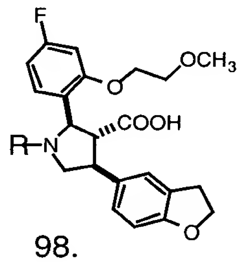
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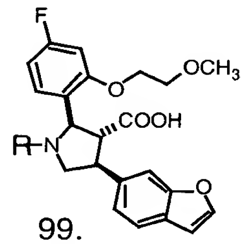
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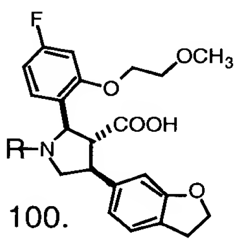
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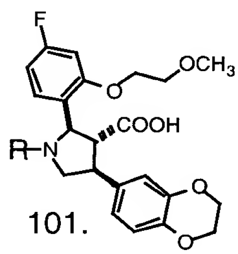
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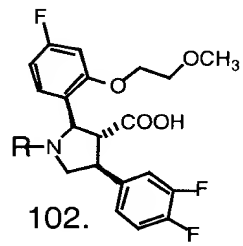
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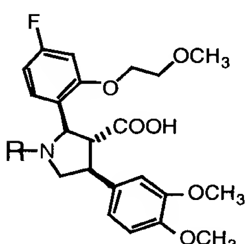
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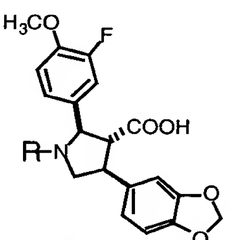
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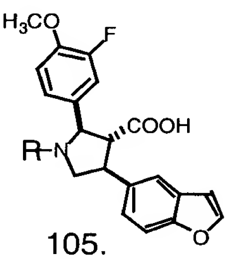
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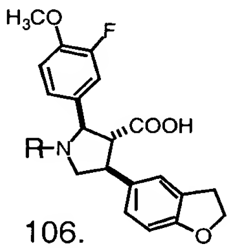
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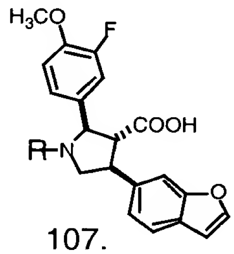
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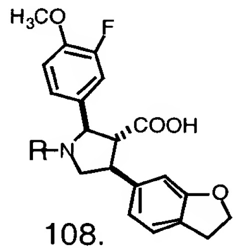
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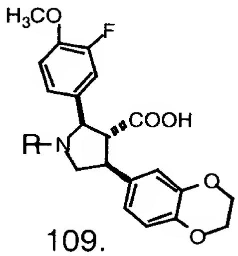
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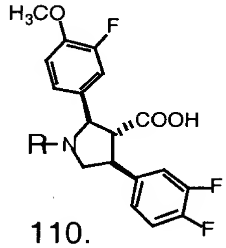
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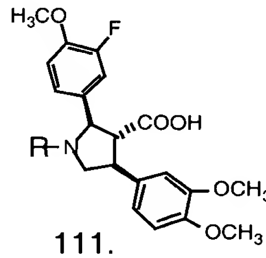
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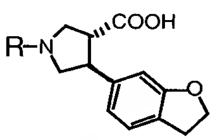
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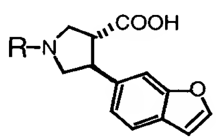
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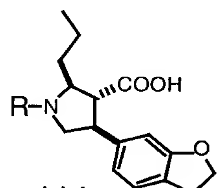
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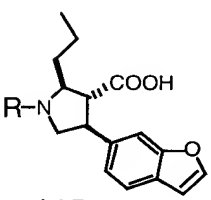
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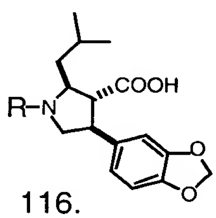
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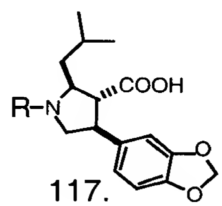
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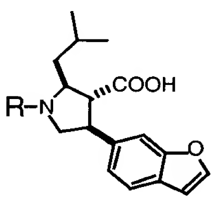
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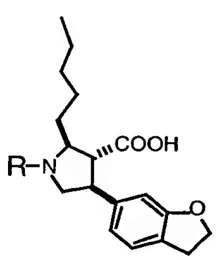
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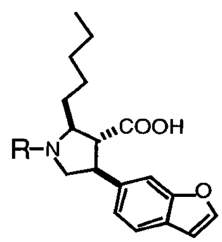
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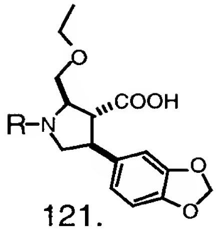

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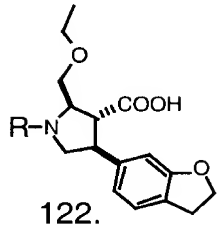

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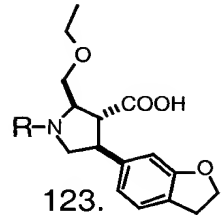

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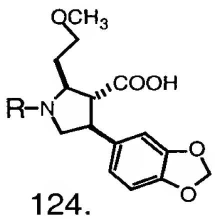

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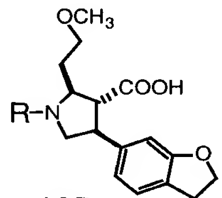

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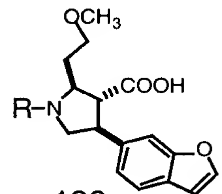

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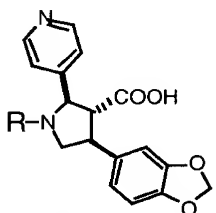

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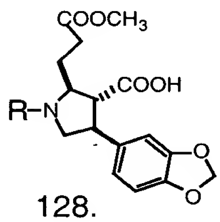

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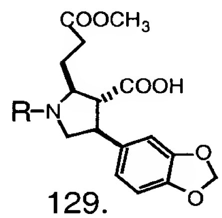

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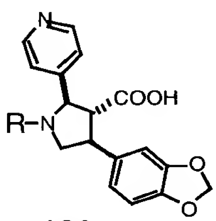

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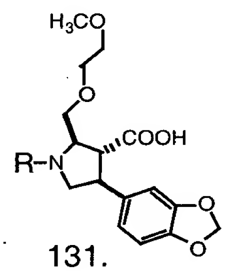

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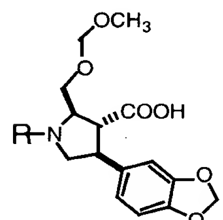

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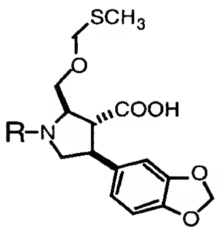

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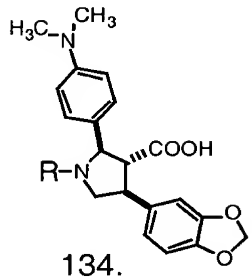

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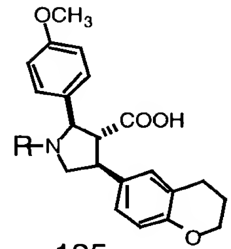

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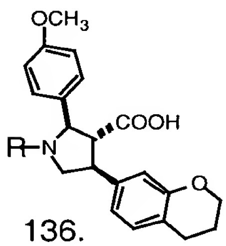

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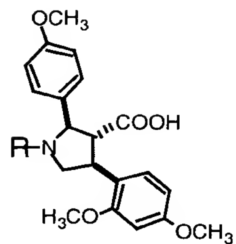

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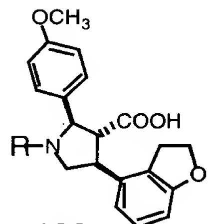

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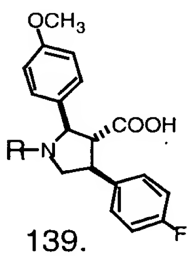

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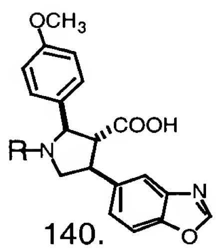

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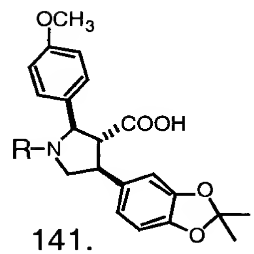

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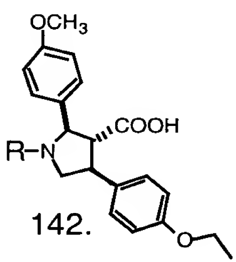

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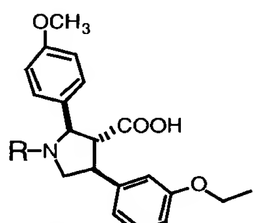

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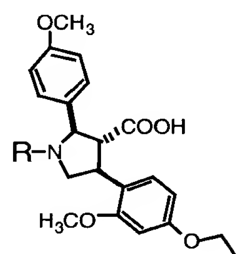

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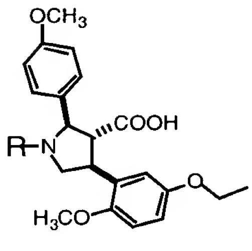

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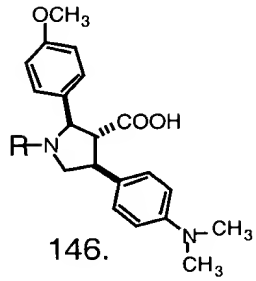

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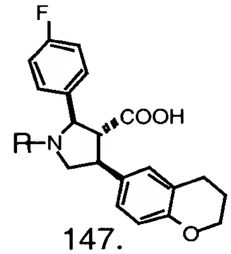

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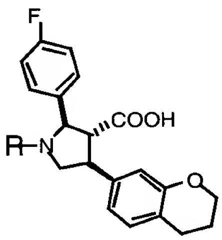

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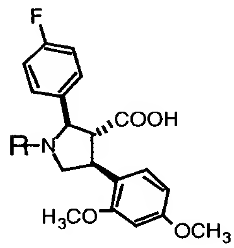

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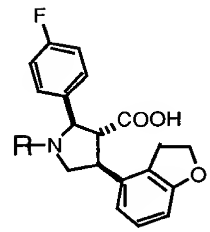

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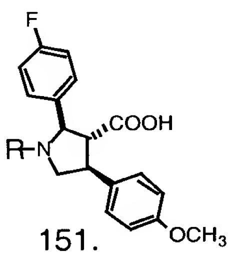

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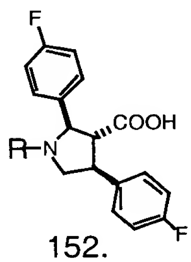

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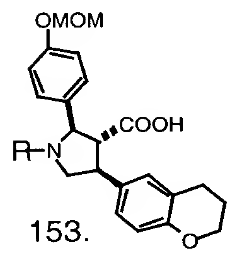

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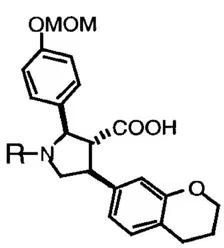

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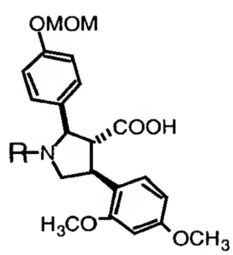

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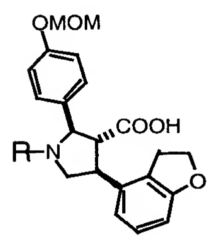

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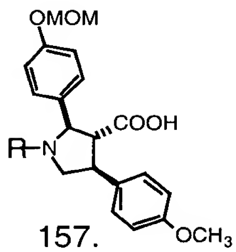
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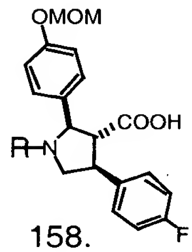
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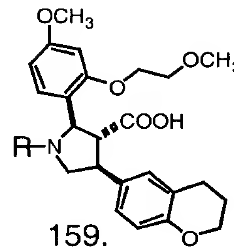
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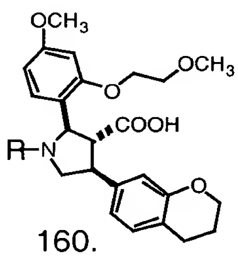
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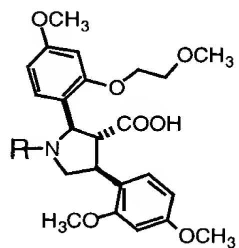
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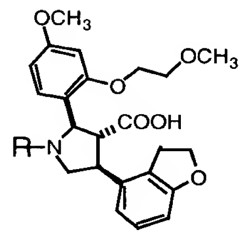
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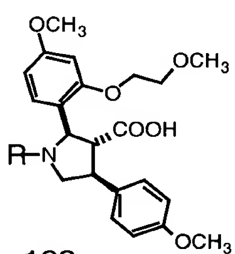
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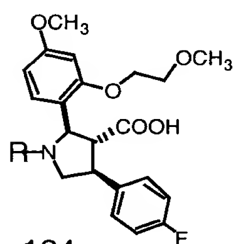
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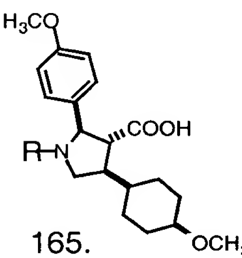
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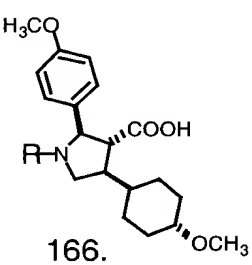
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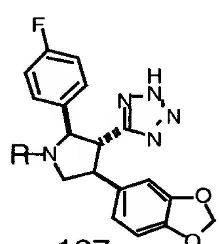
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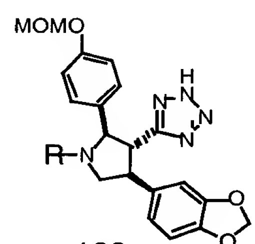
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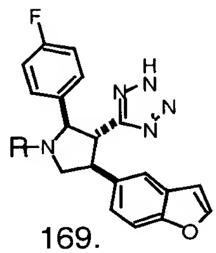
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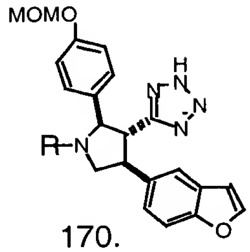
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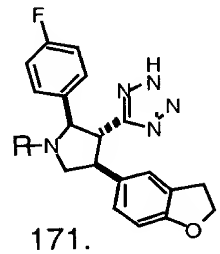
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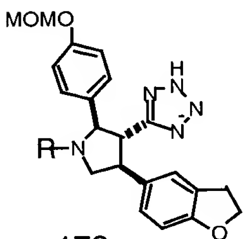
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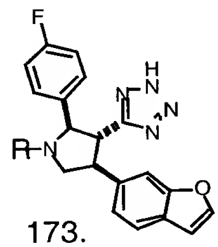
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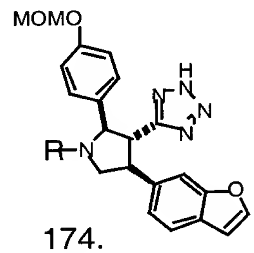
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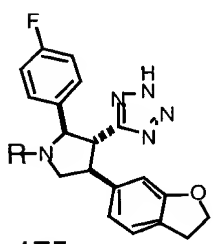
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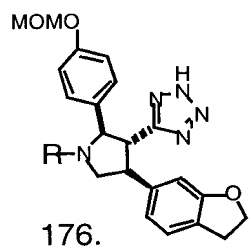
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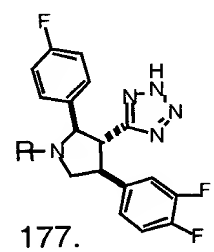
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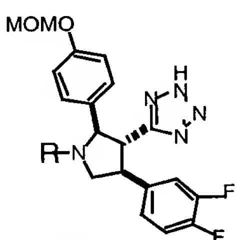
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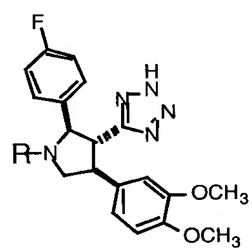
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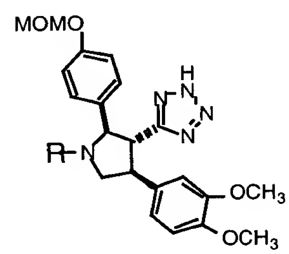
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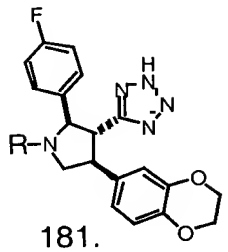

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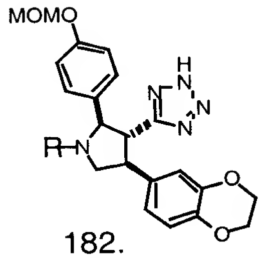

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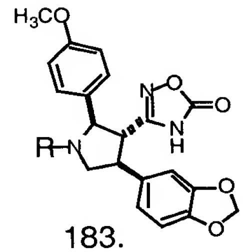

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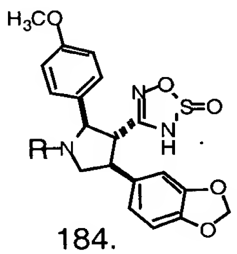

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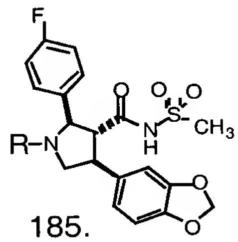

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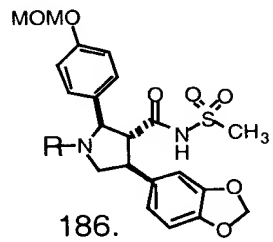

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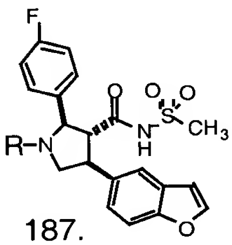

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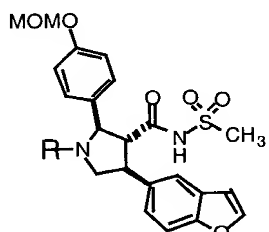

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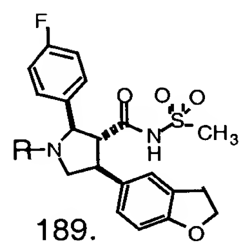

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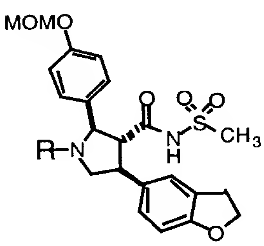

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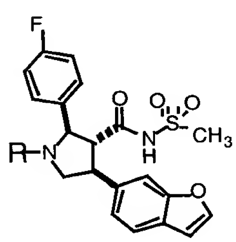

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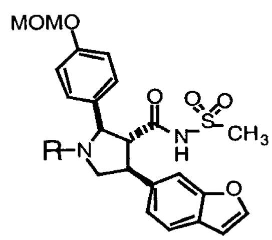

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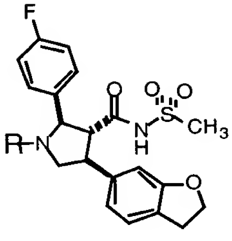

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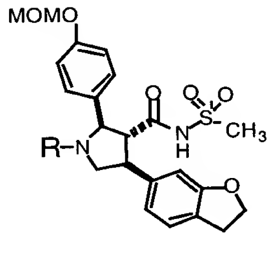

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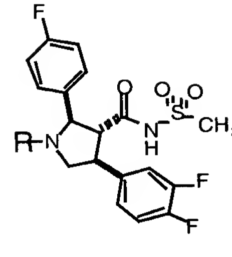

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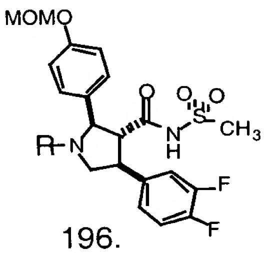

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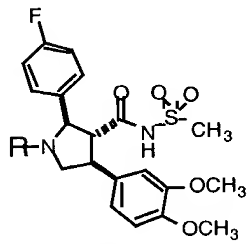

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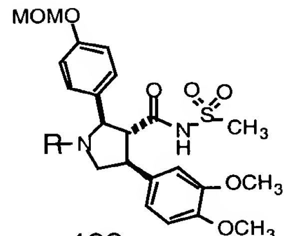

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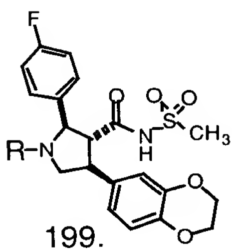

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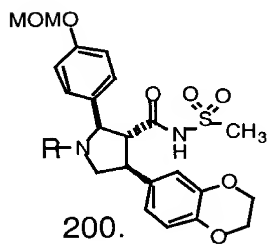

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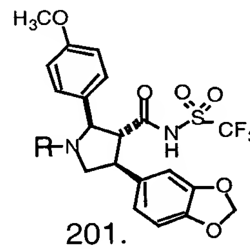

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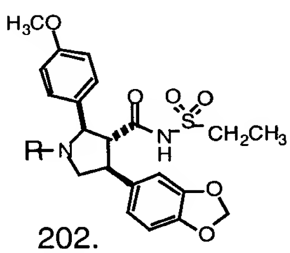

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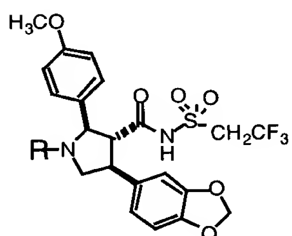

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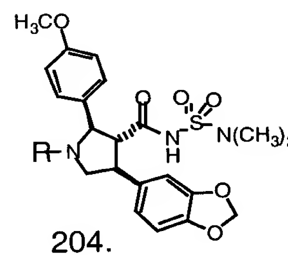

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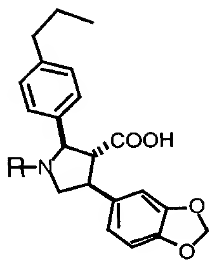

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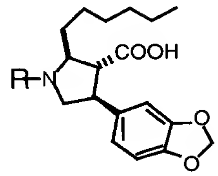

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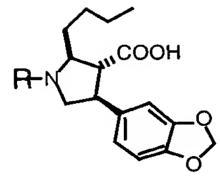

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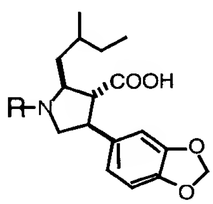

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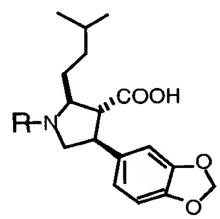

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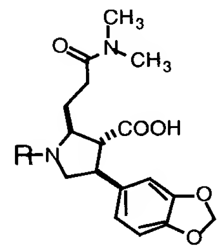

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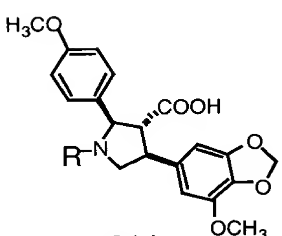

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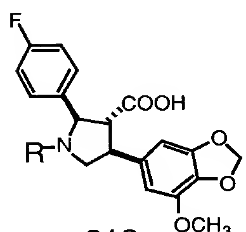

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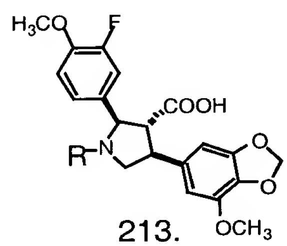

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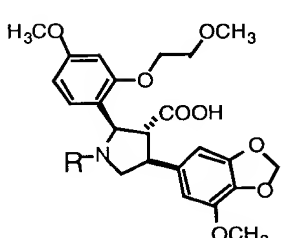

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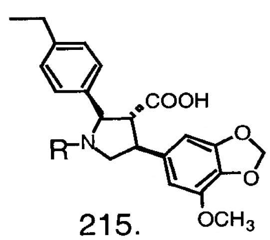

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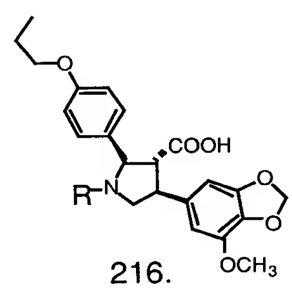

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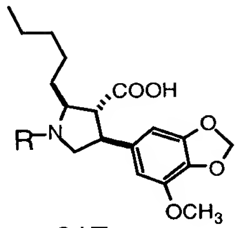

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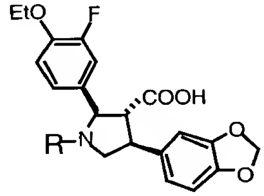

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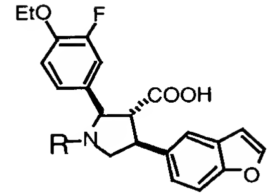

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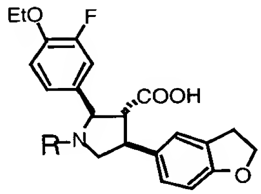

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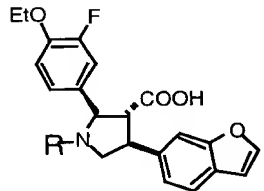

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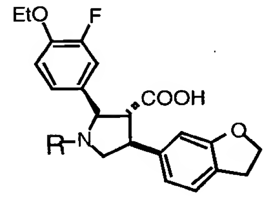

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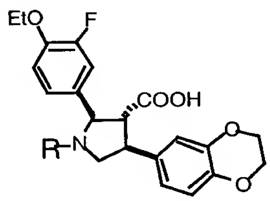

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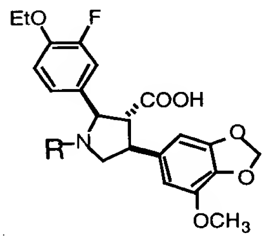

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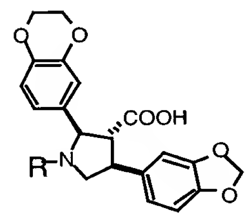

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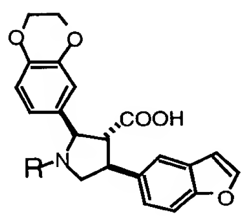

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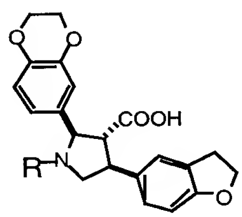

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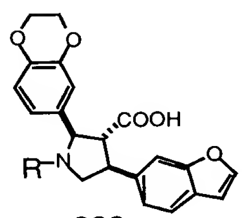

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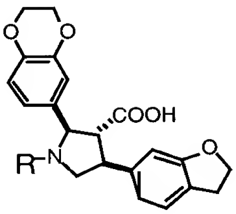

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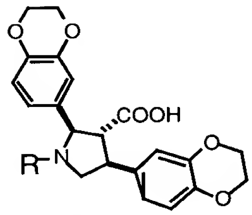

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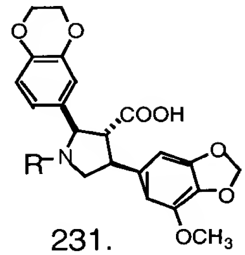

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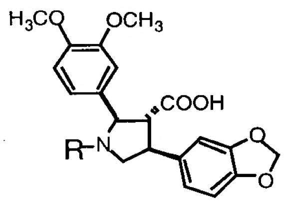

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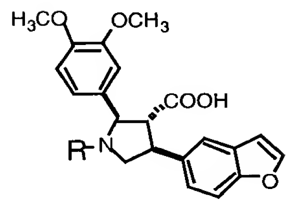

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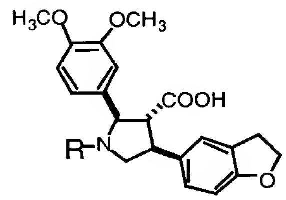

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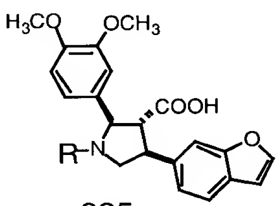

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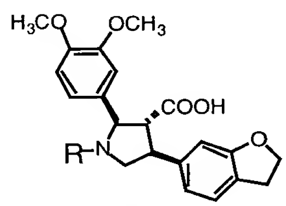

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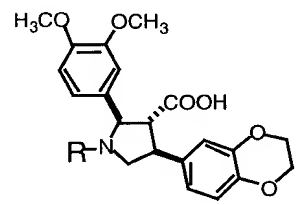

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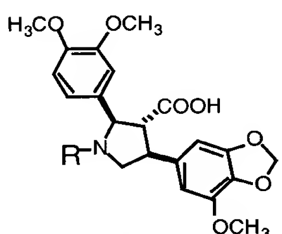

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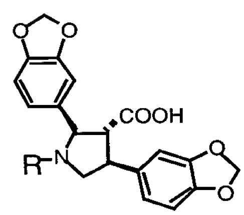

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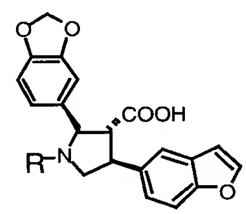

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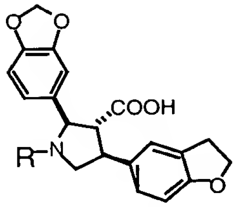

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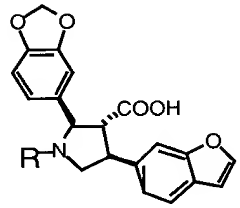

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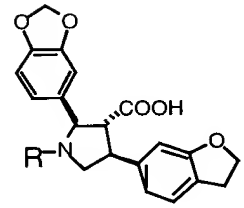

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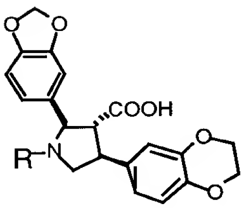

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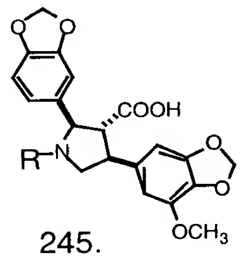

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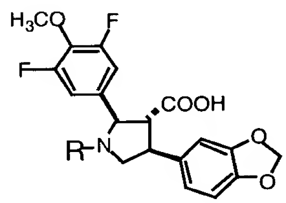

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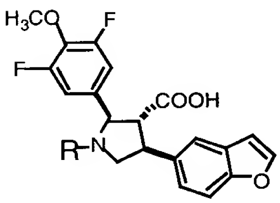

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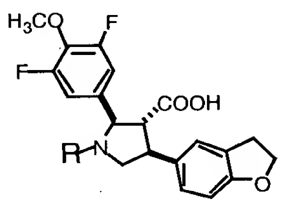

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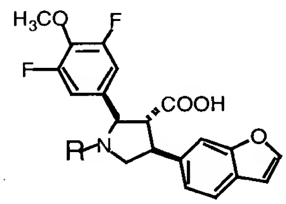

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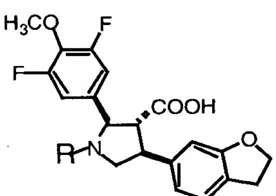

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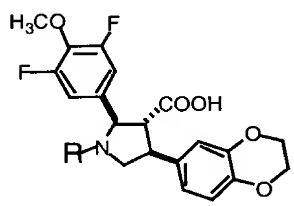

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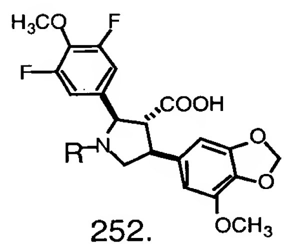

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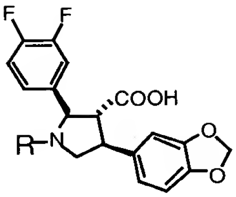

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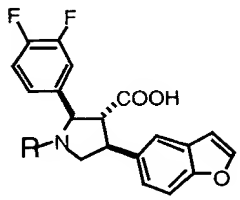

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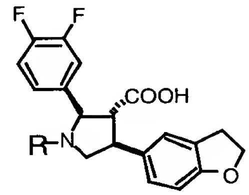

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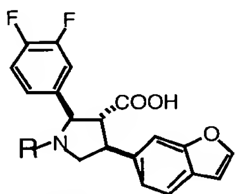

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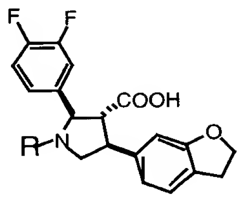

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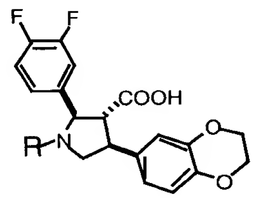

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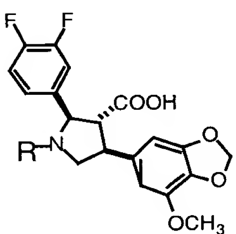

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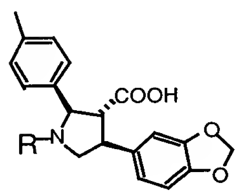

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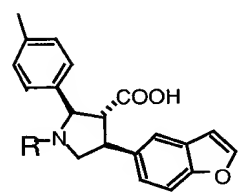

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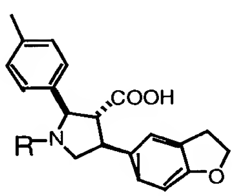

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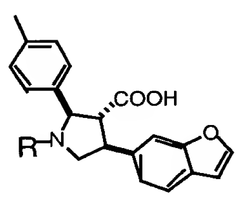

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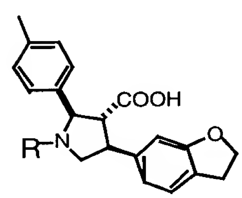

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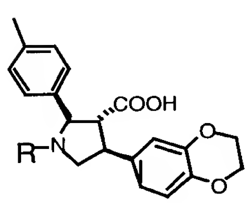

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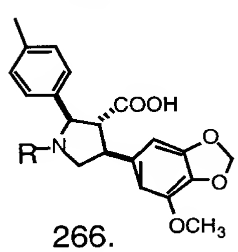

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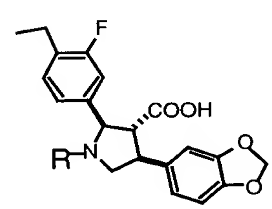

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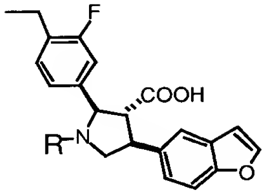

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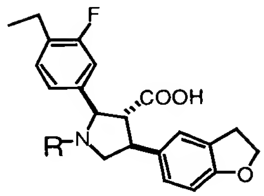

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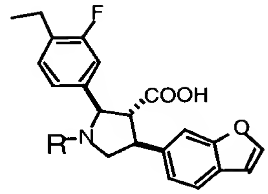

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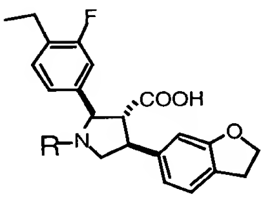

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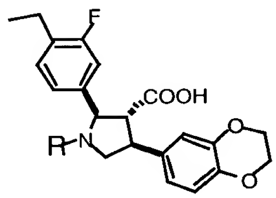

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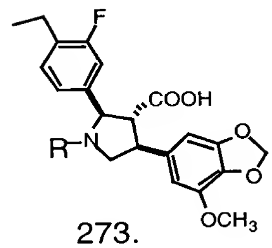

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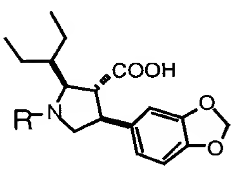

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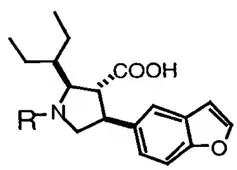

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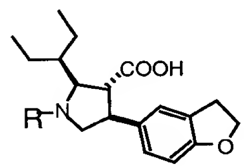

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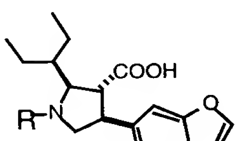

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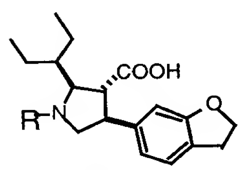

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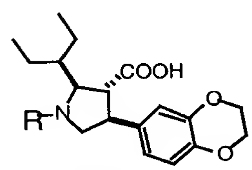

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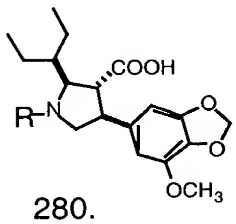

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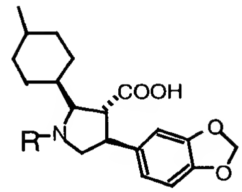

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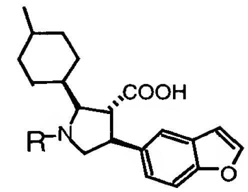

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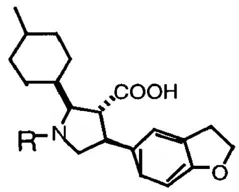

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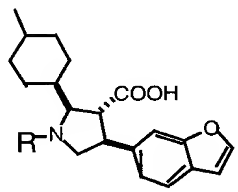

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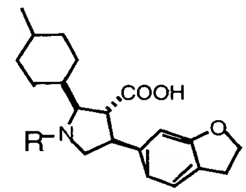

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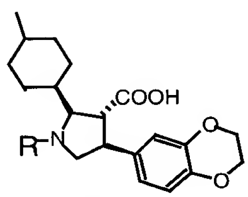

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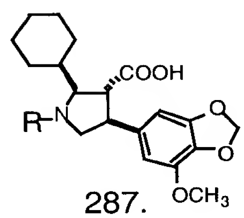

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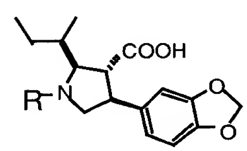

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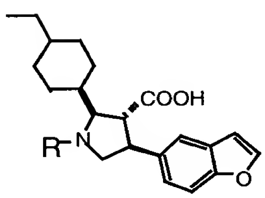

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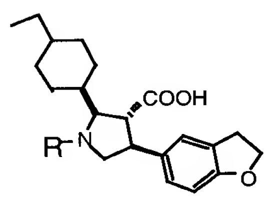

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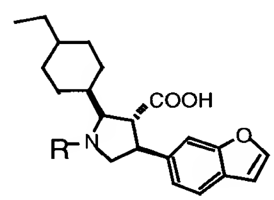

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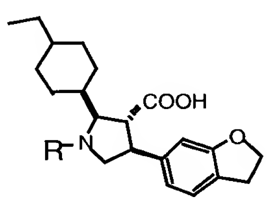

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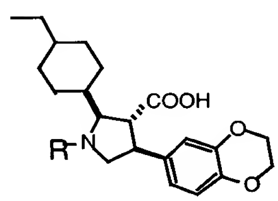

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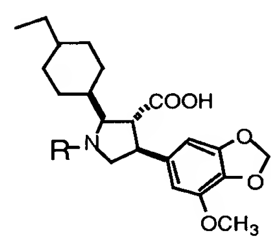

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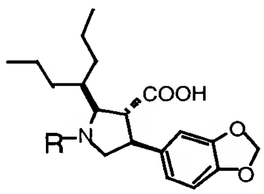

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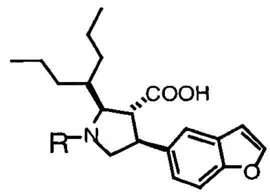

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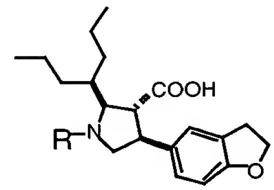

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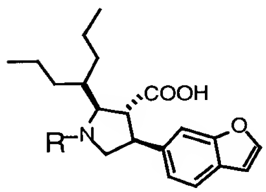

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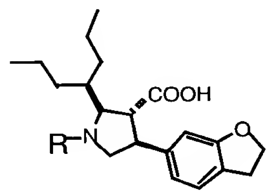

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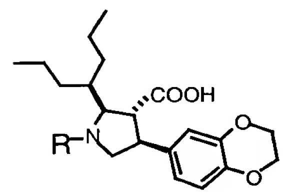

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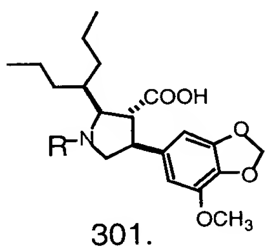

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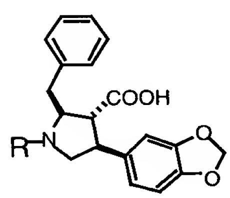

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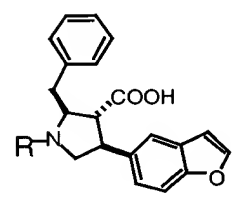

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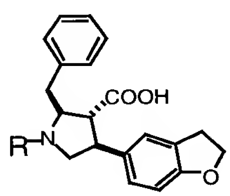

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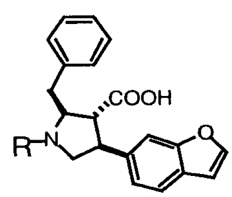

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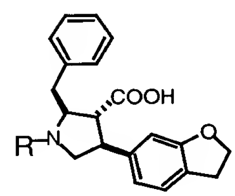

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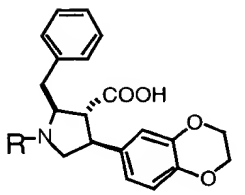

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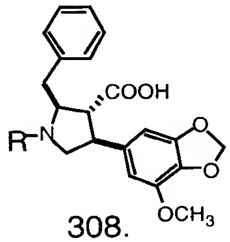

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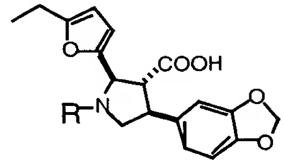

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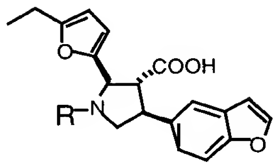

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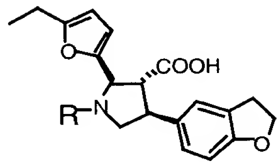

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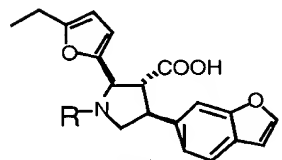

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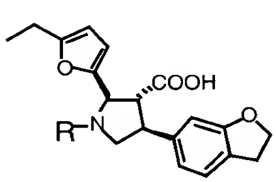

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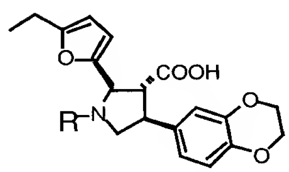

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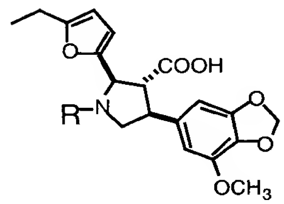

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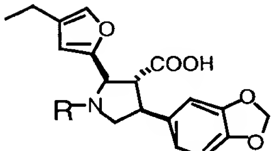

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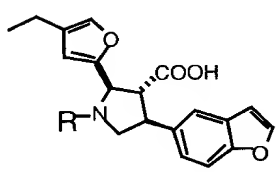

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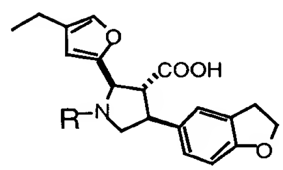

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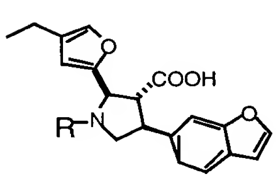

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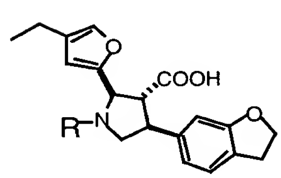

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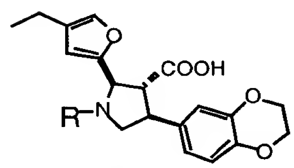

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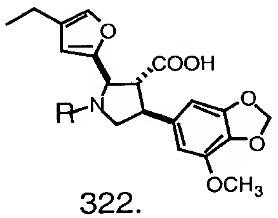
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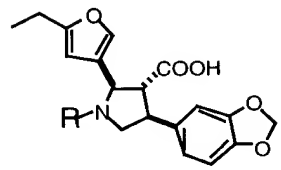
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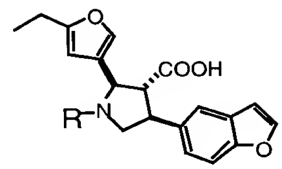
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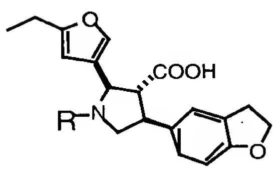
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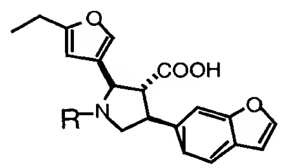
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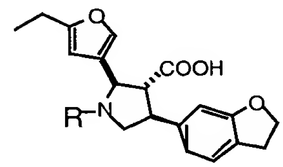
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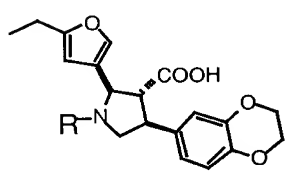
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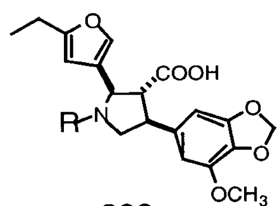
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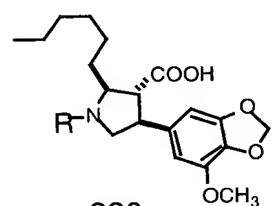
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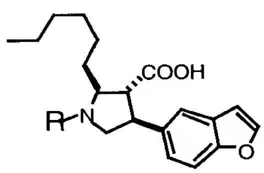
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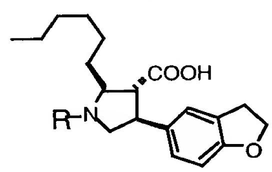
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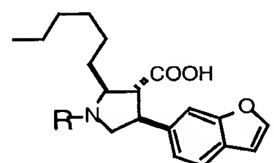
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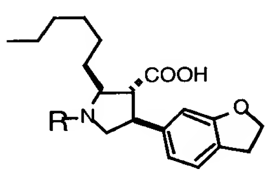
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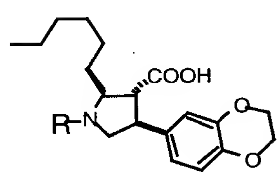
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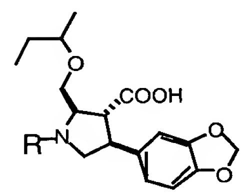
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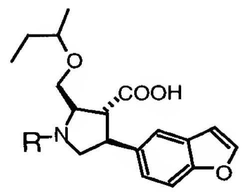

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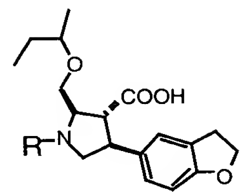

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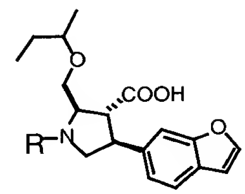

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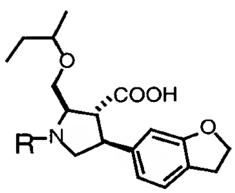

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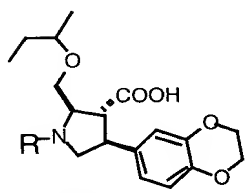

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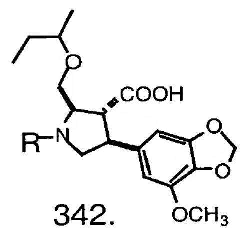

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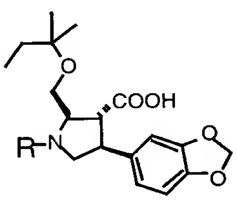

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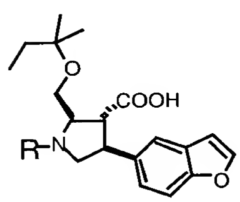

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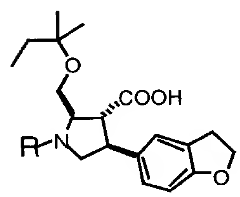

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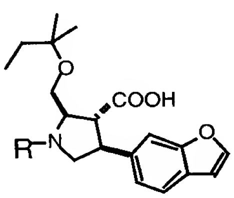

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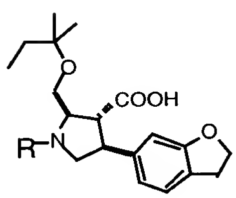

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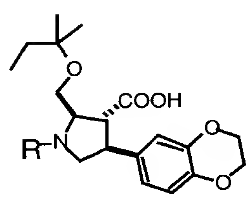

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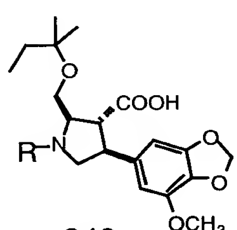

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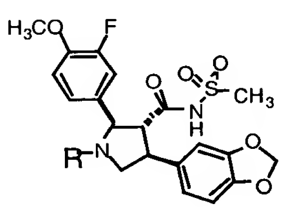

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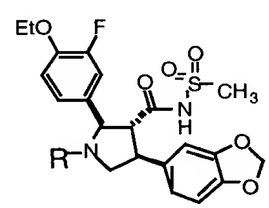

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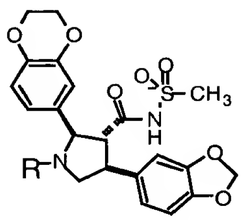

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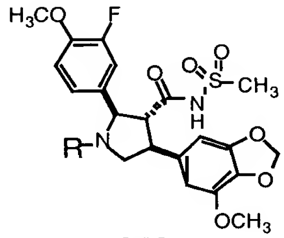

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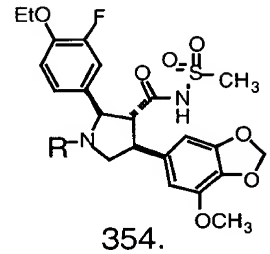

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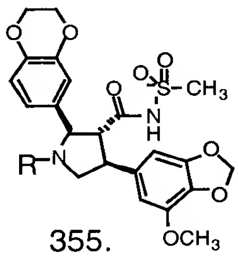

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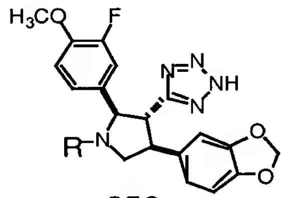

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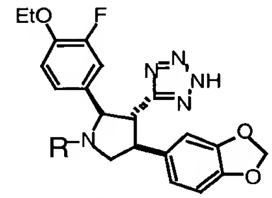

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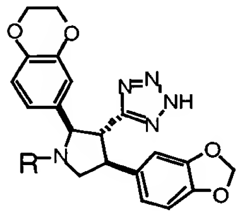

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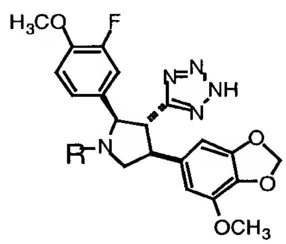

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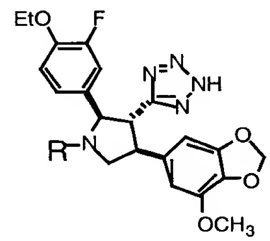

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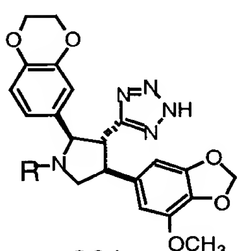

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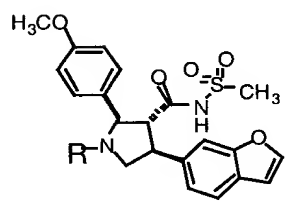

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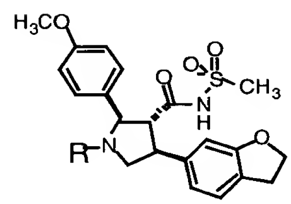

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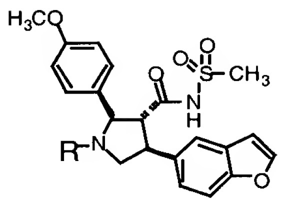

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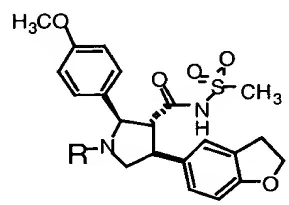

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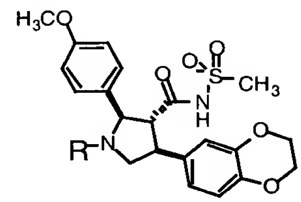

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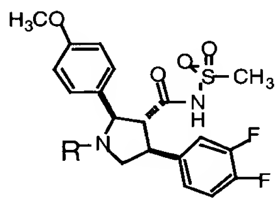

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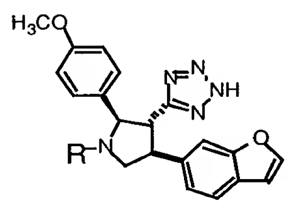

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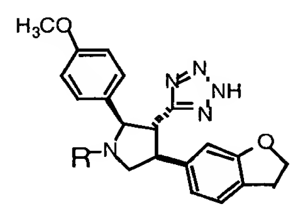

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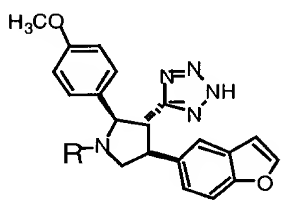

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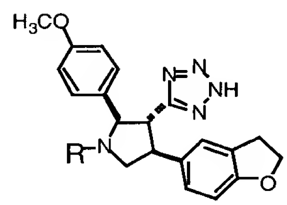

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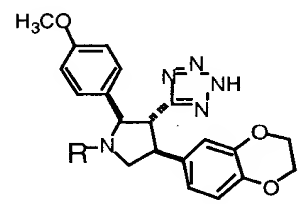

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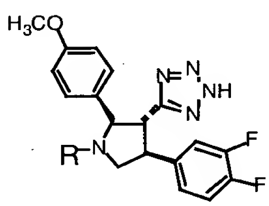

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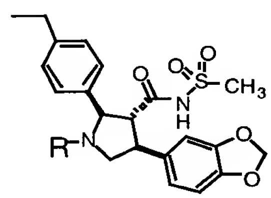

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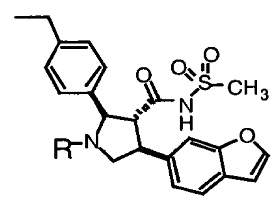

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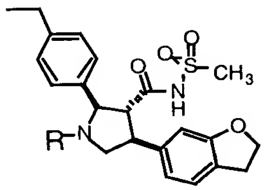

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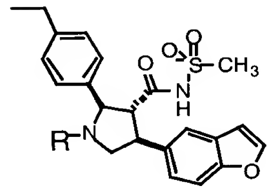

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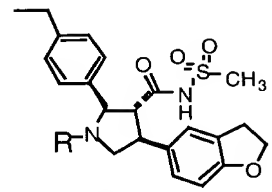

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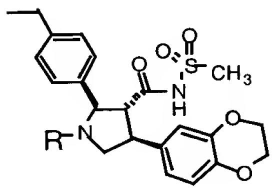

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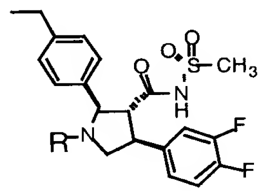

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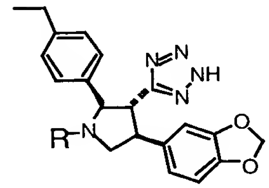

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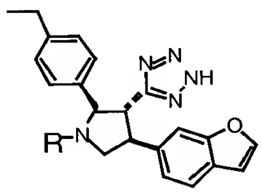

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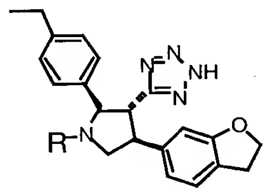

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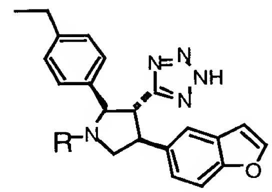

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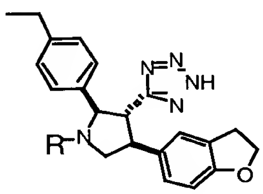

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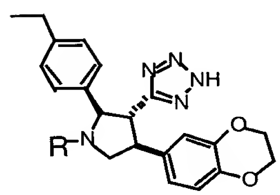

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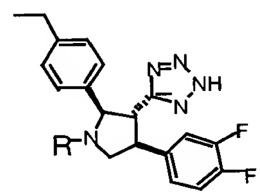

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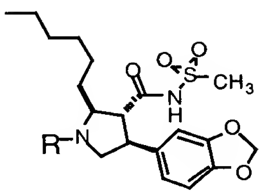

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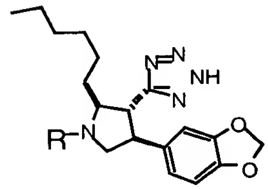

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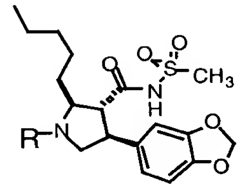

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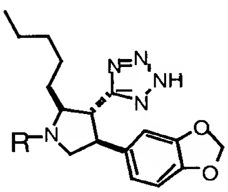

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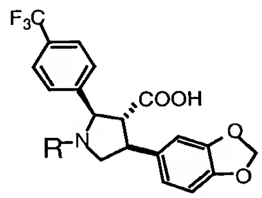

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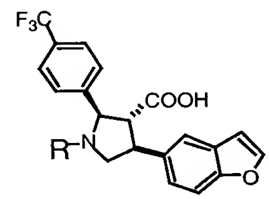

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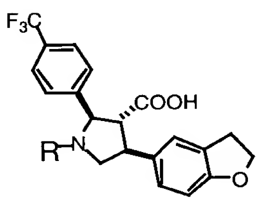

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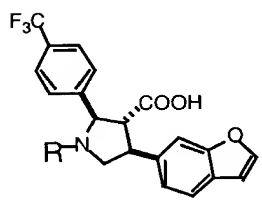

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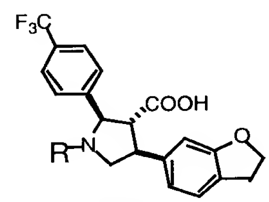

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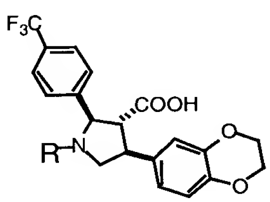

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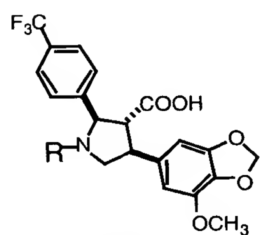

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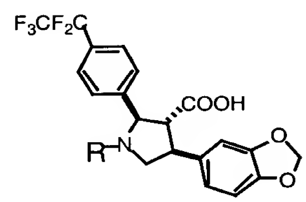

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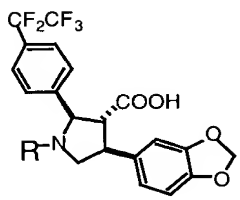
Table 2A cont.



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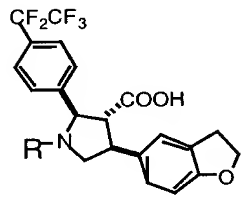

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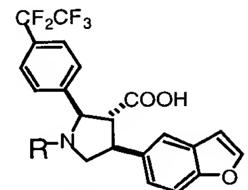

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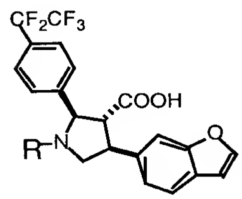

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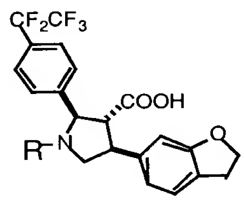

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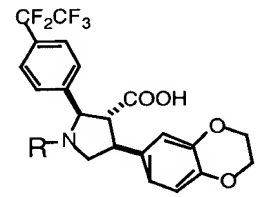

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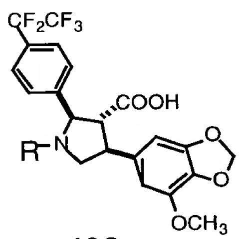

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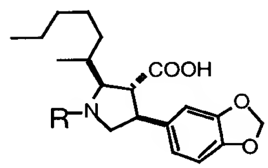

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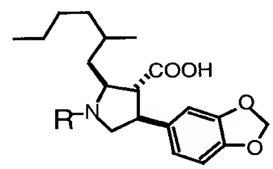

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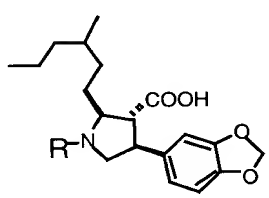

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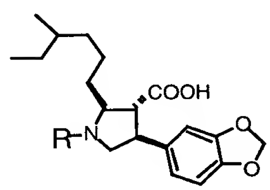

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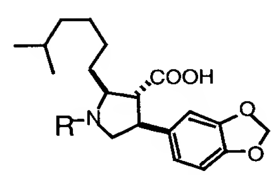

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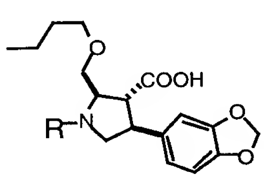

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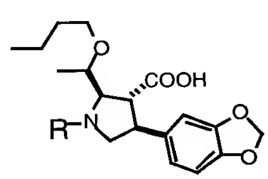

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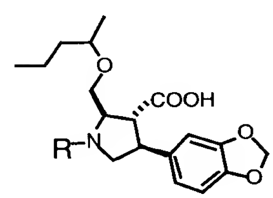

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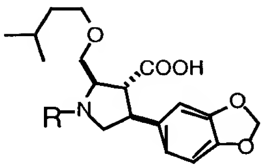

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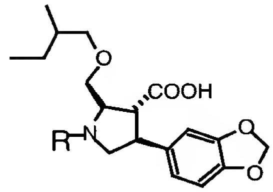

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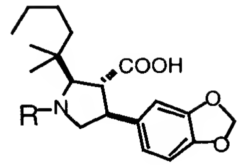

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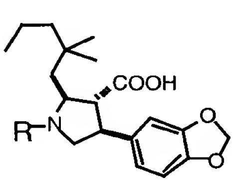

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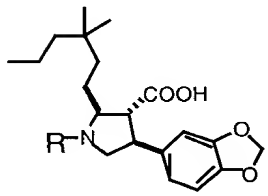

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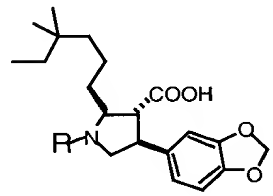

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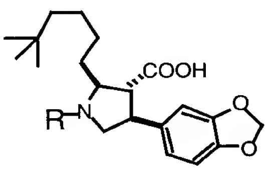

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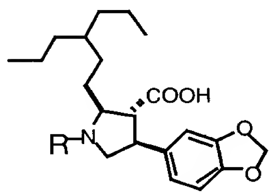

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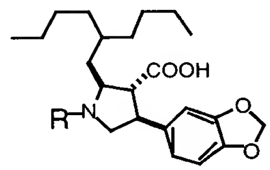

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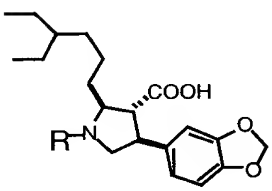

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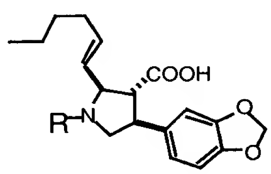

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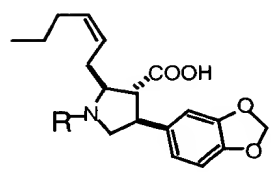

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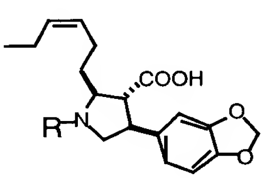

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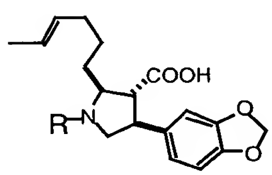

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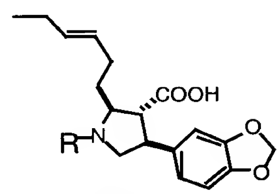

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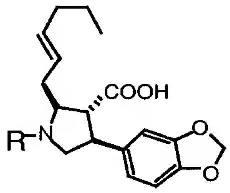

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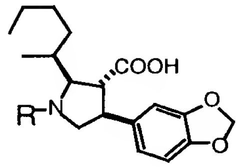

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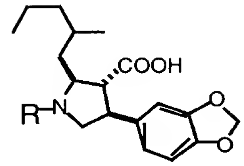

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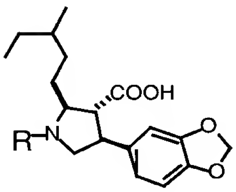

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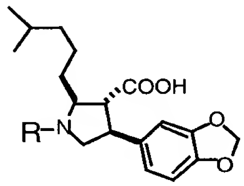

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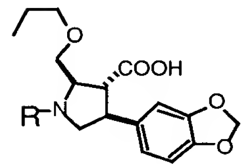

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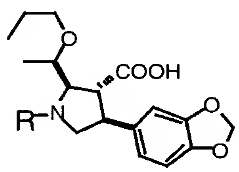

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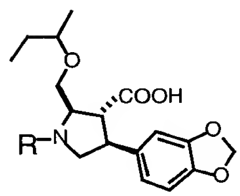

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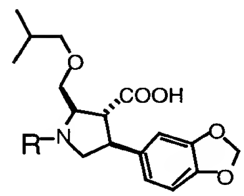

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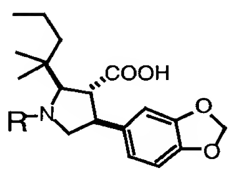

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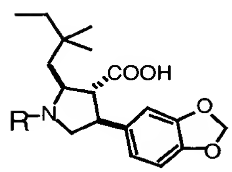

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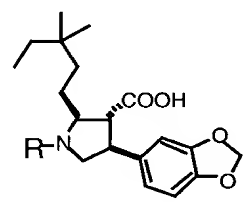

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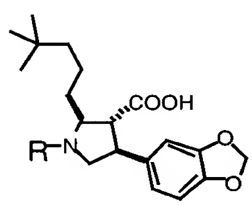

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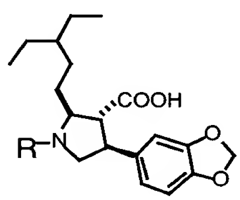

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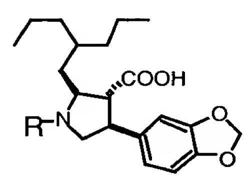

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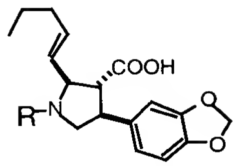

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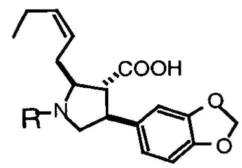

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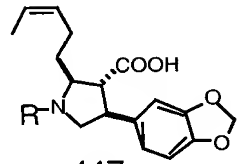

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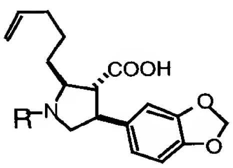

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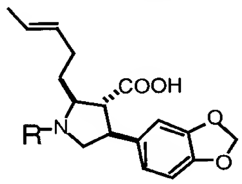

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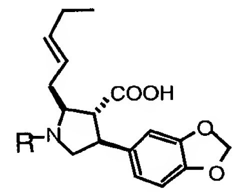

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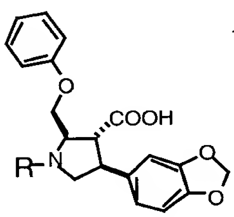

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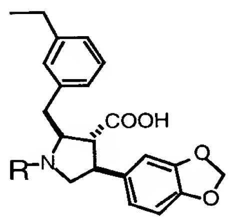

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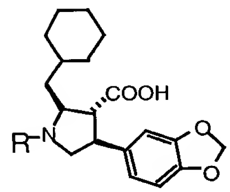

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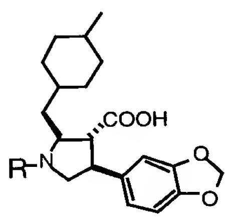

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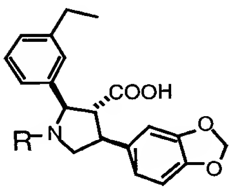

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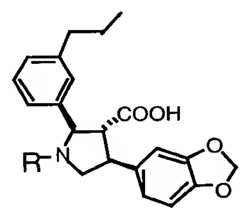

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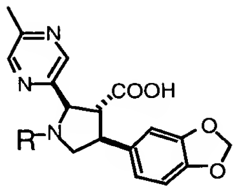

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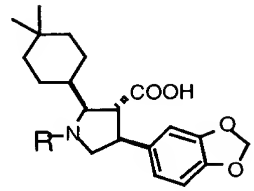

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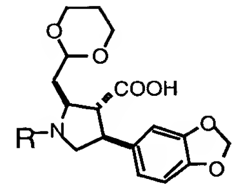

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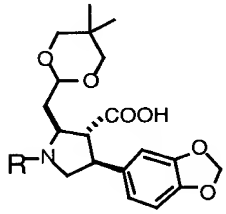

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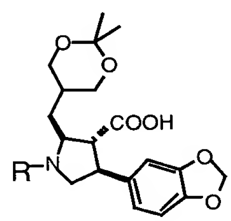

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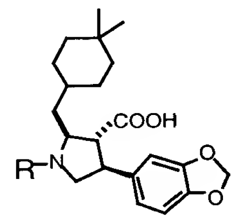

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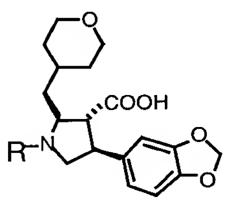

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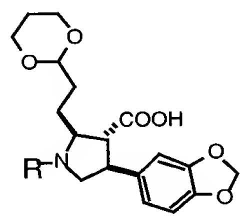

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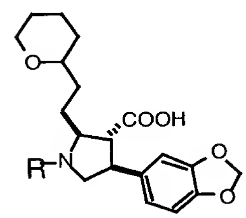

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Table 2B

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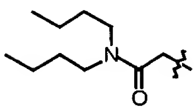

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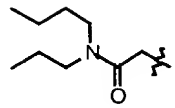

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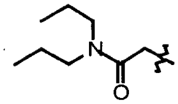

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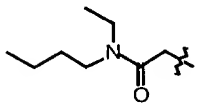

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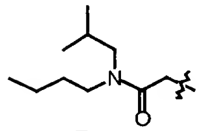

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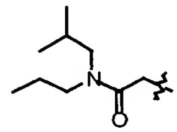

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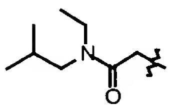

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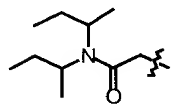

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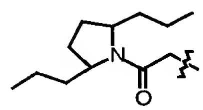

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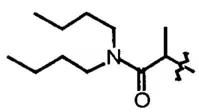

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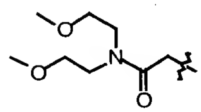

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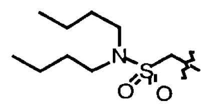

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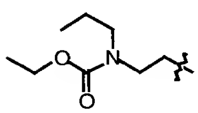

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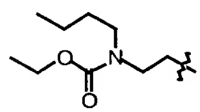

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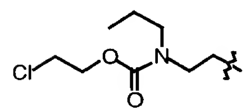

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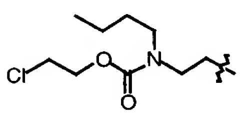

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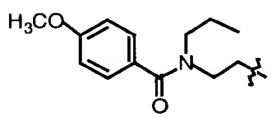

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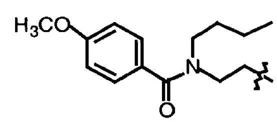

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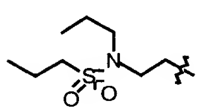

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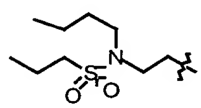

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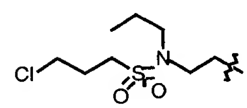
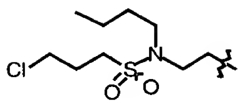


21.

Table 2B cont.

R **R** **R**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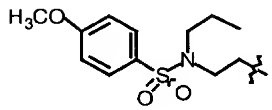
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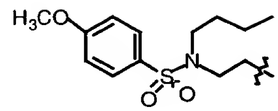
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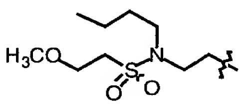
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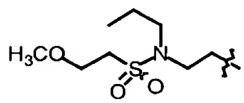
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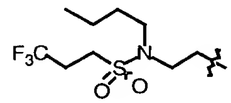
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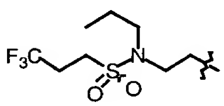
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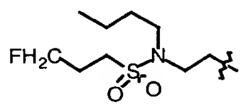
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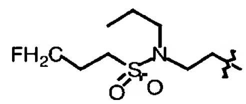
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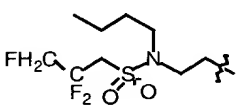
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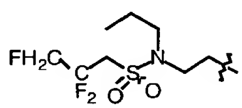
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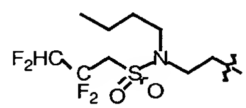
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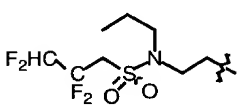
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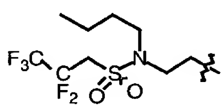
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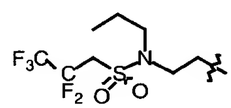
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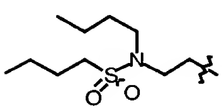
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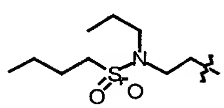
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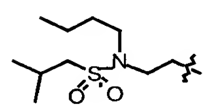
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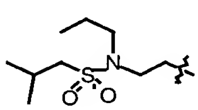
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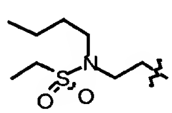
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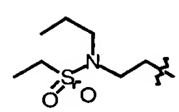
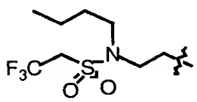

42.

Table 2B cont.

R	R	R



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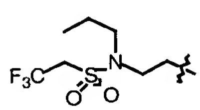

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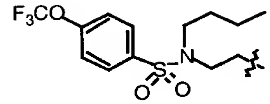

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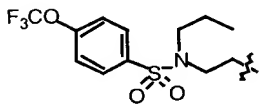

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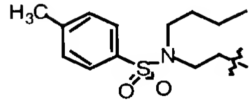

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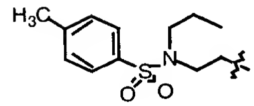

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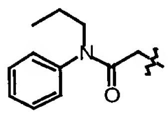

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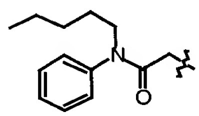

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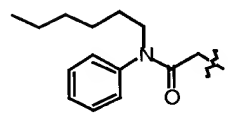

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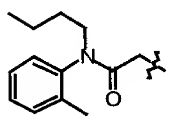

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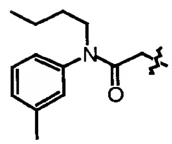

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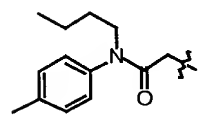

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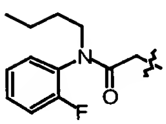

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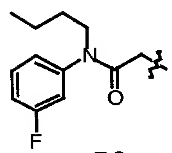

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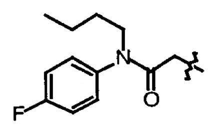

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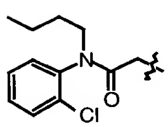

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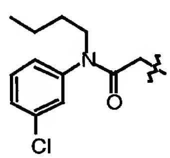

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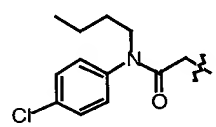
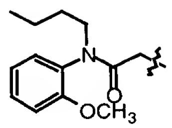


60.

Table 2B cont.

R | **R** | **R**



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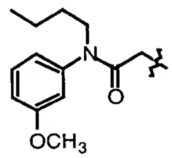

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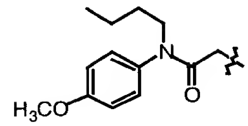

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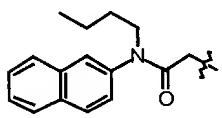

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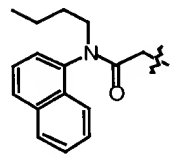

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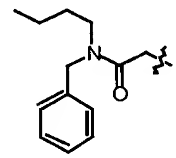

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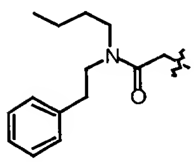

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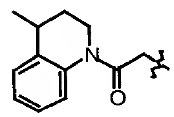

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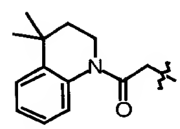

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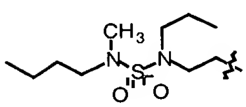

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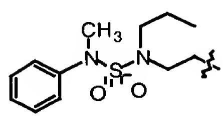

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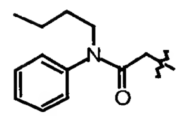

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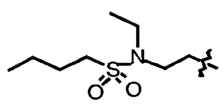

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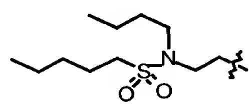

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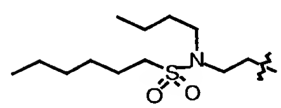

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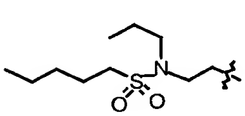

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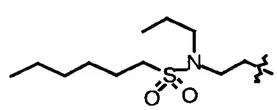

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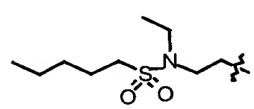
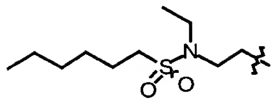


78.

Table 2B cont.

R	R	R



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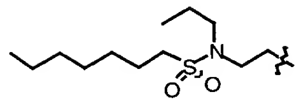

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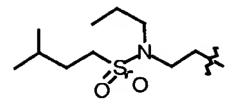

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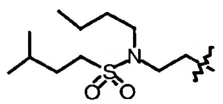

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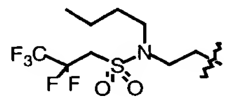
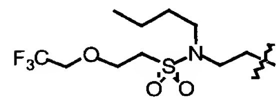


83.



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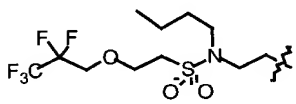

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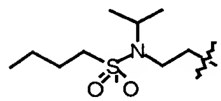

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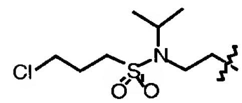

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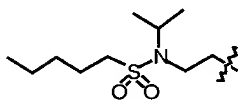

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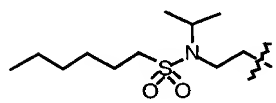

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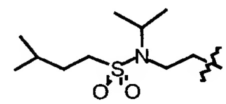

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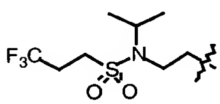

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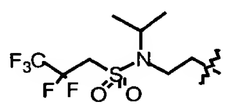

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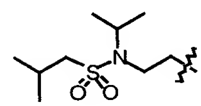

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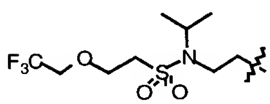

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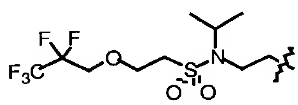

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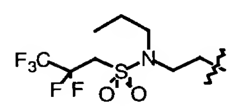

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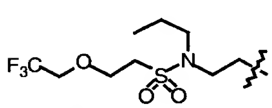

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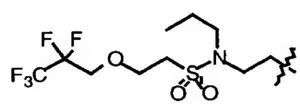

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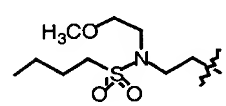

99.

Table 2B cont.

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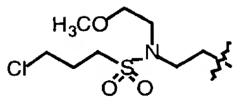
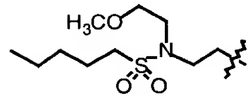
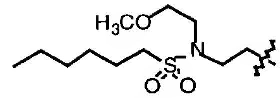
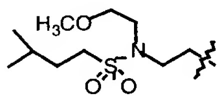
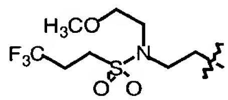
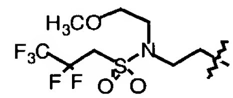
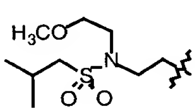
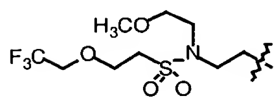
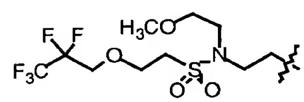
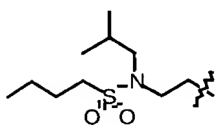
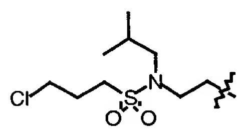
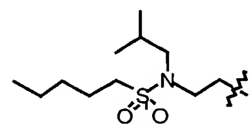
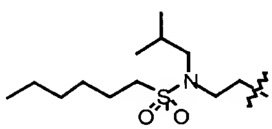
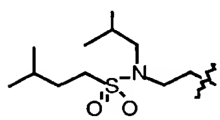
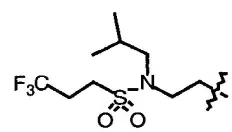
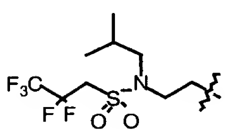
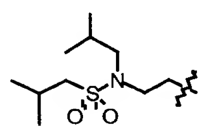
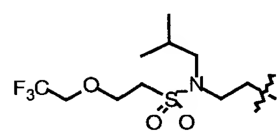
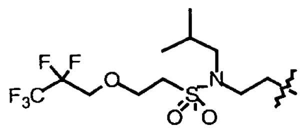
 100.	 101.	 102.
 103.	 104.	 105.
 106.	 107.	 108.
 109.	 110.	 111.
 112.	 113.	 114.
 115.	 116.	 117.

Table 2B cont.

R | R | R



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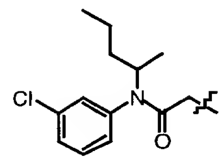

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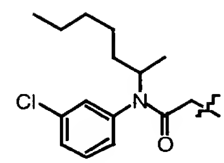

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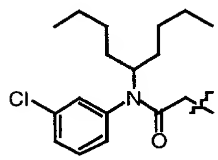

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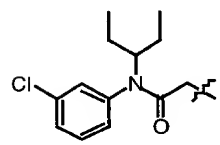

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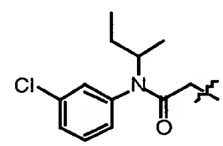

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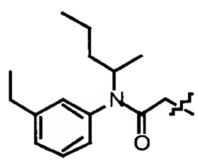

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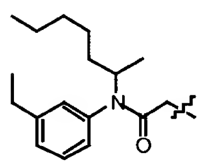

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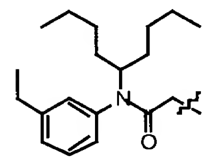

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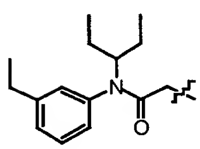

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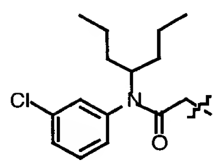

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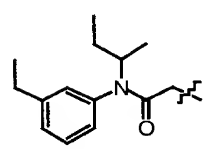

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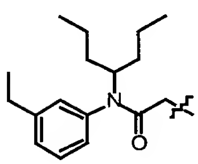

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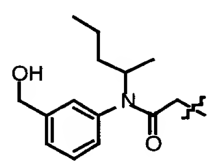

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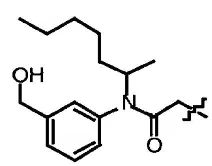
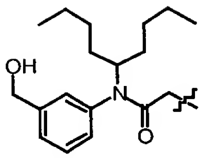


132.

Table 2B cont.

R **R** **R**



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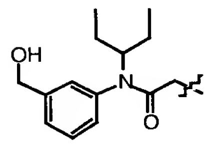

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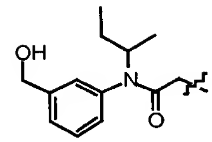

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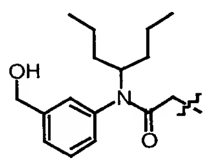

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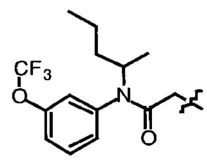

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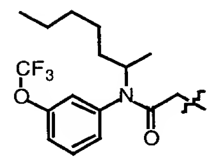

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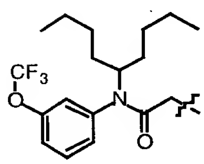

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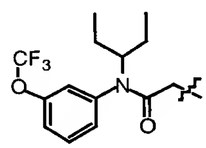

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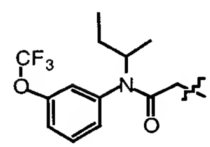

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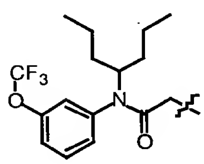

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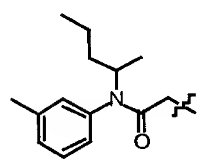

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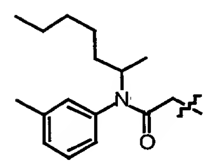

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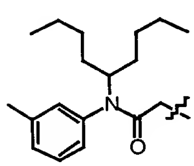

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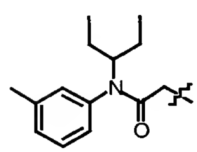

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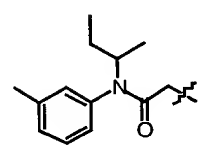
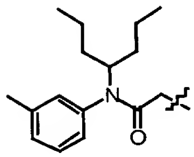
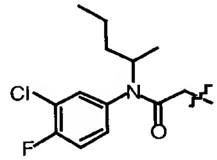
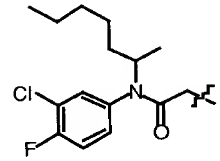
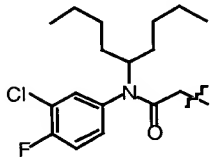
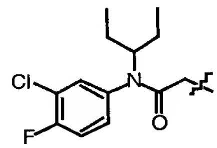
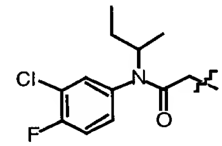
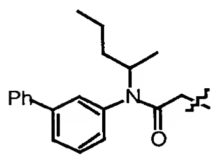
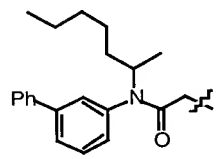
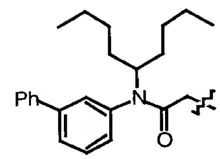
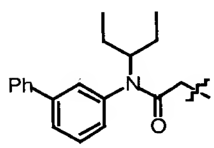
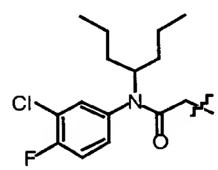
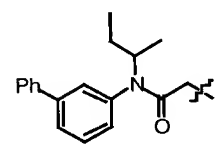
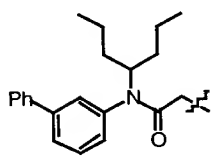
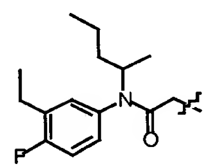
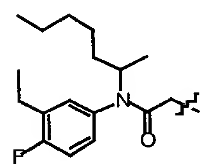


147.

Table 2B cont.

R	R	R
 148.	 149.	 150.
 151.	 152.	 153.
 154.	 155.	 156.
 157.	 158.	 159.
 160.	 161.	 162.

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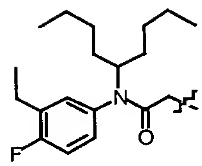
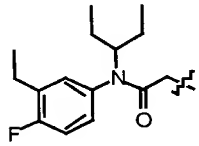
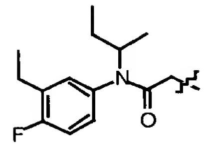
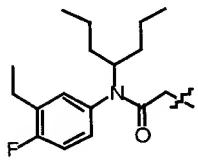
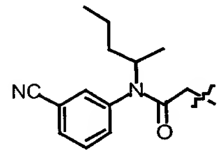
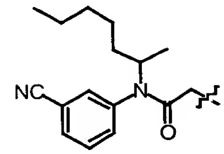
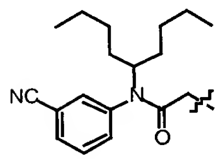
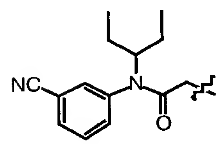
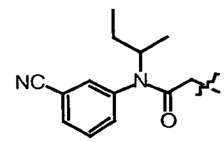
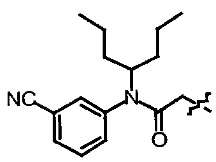
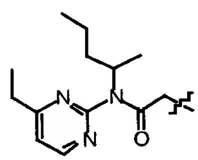
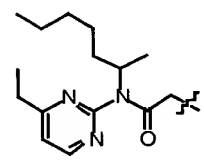
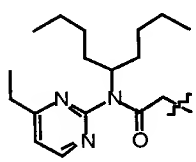
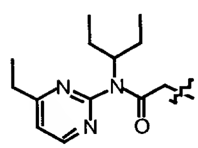
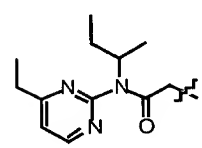
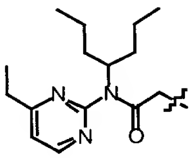
 163.	 164.	 165.
 166.	 167.	 168.
 169.	 170.	 171.
 172.	 173.	 174.
 175.	 176.	 177.

Table 2B cont.

R **R** **R**



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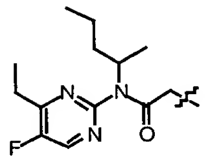

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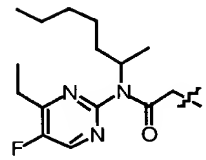

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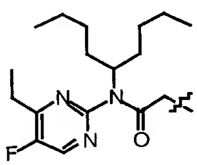

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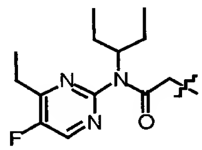

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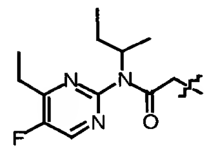

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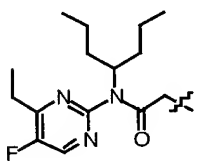

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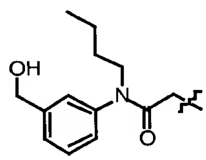

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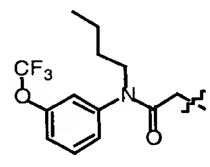

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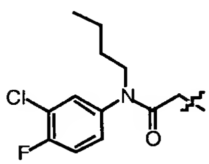

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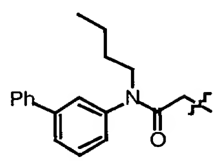

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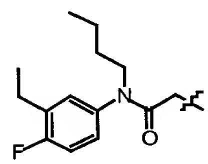

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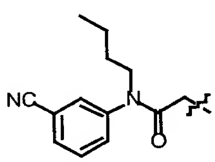

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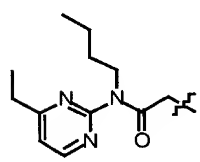

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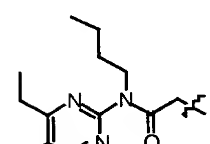
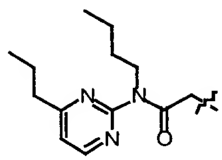


192.

Table 2B cont.

R | **R** | **R**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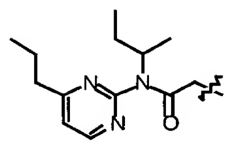
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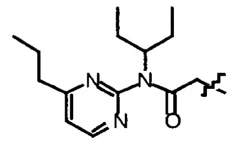
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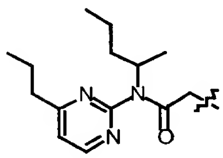
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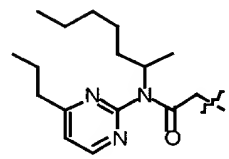
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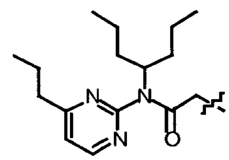
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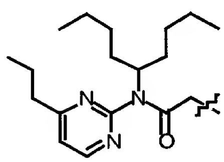
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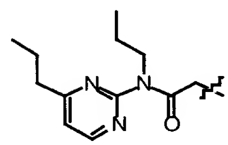
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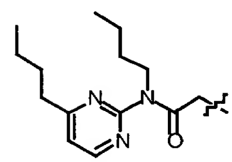
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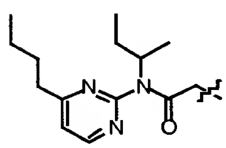
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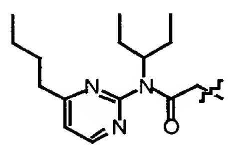
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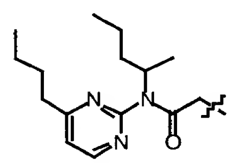
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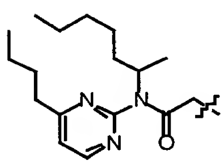
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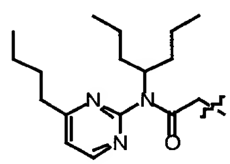
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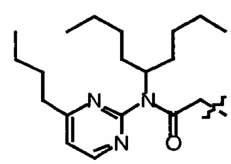
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Table 2B cont.

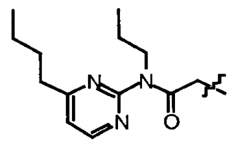
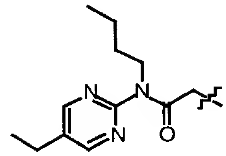
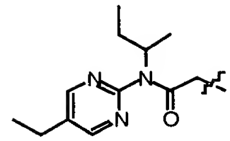
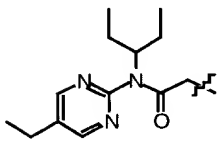
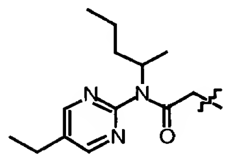
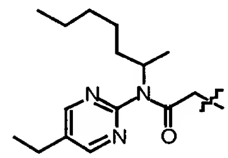
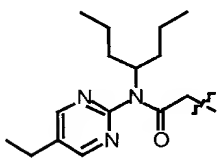
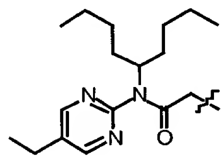
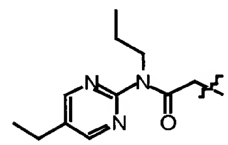
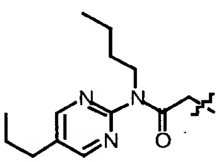
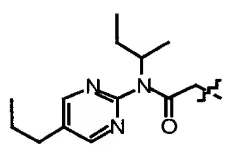
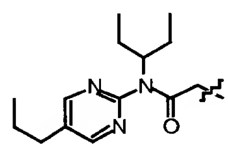
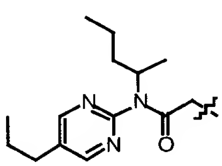
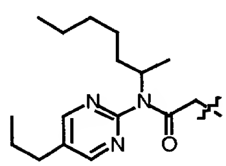
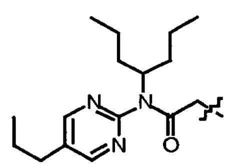
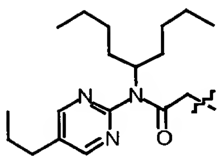
R	R	R
 208.	 209.	 210.
 211.	 212.	 213.
 214.	 215.	 216.
 217.	 218.	 219.
 220.	 221.	 222.

Table 2B cont.

R **R** **R**



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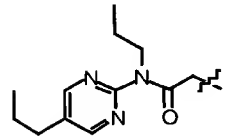

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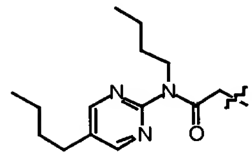

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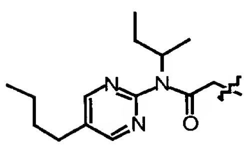
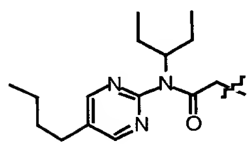


226.



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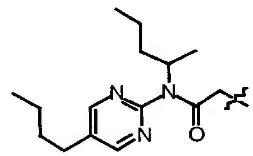

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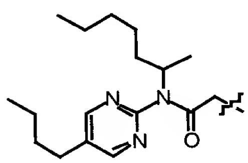

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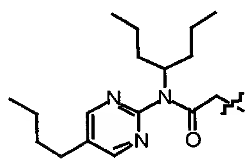

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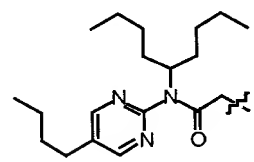

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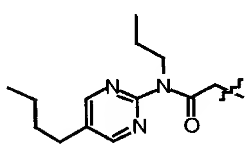

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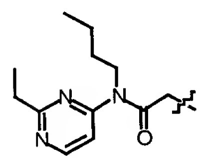

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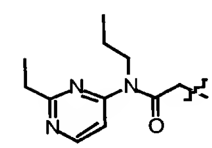

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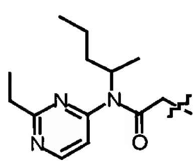

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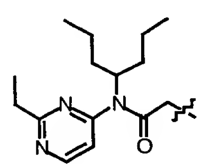

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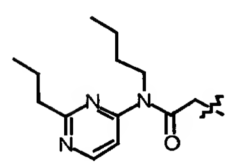

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Table 2B cont.

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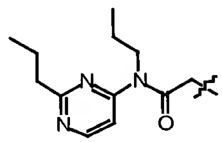
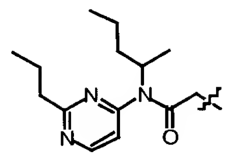
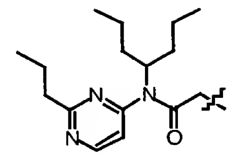
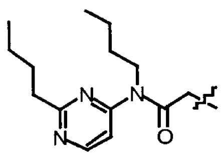
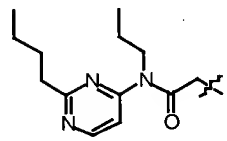
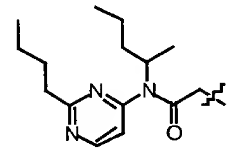
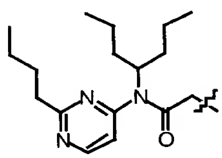
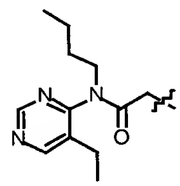
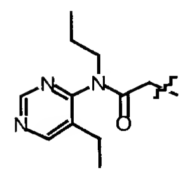
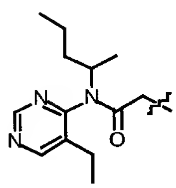
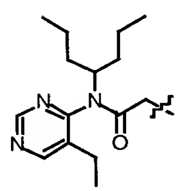
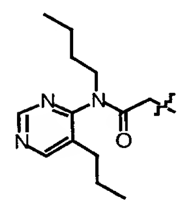
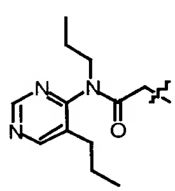
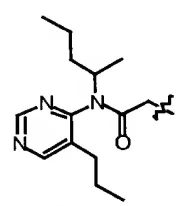
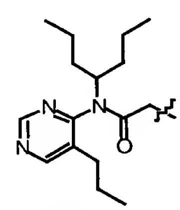
 238.	 239.	 240.
 241.	 242.	 243.
 244.	 245.	 246.
 247.	 248.	 249.
 250.	 252.	 252.

Table 2B cont.

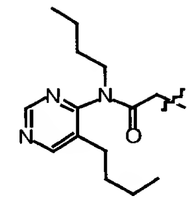
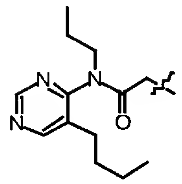
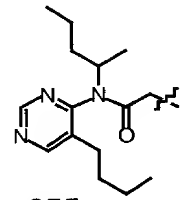
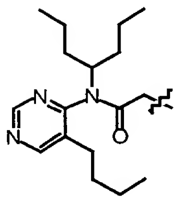
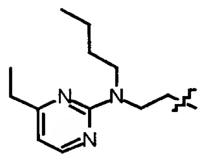
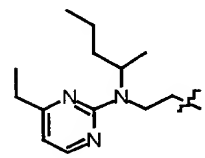
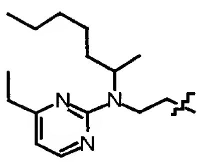
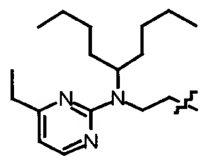
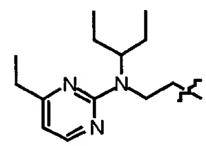
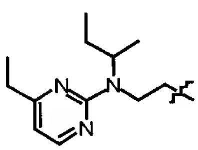
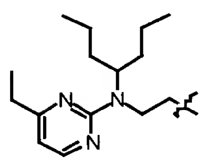
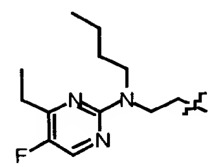
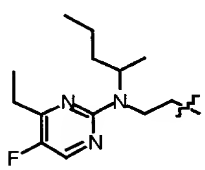
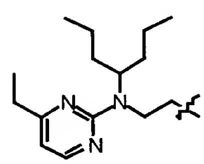
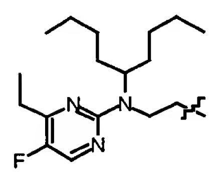
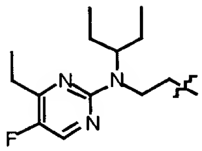
R	R	R
 253.	 254.	 255.
 256.	 257.	 258.
 259.	 260.	 261.
 262.	 263.	 264.
 265.	 266.	 267.

Table 2B cont.

R	R	R



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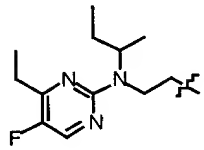

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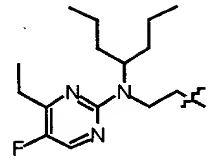

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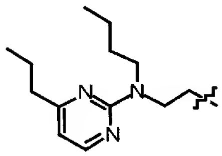

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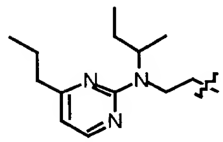

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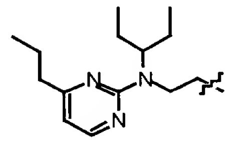

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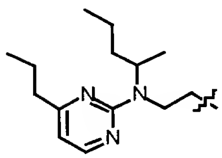

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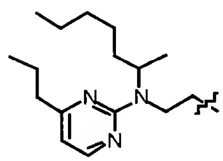

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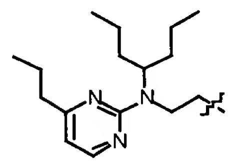

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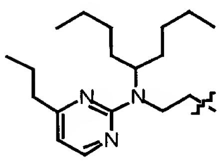

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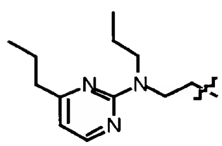

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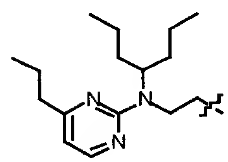

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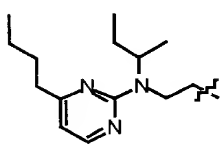

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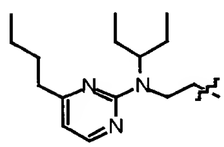

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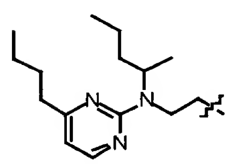
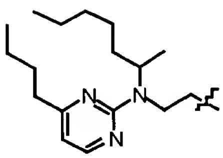


282.

Table 2B cont.

R **R** **R**



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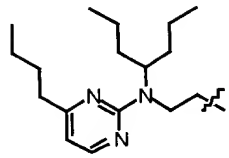

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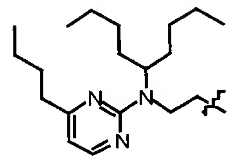

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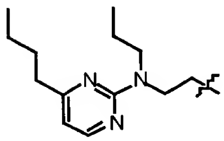

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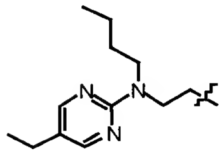

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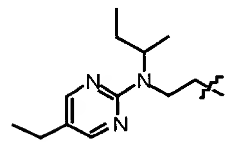

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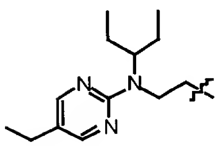

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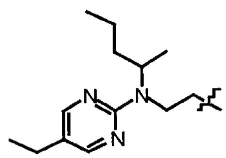

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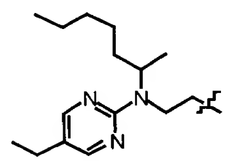

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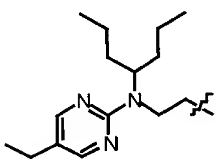

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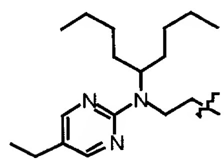

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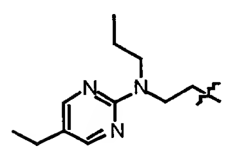

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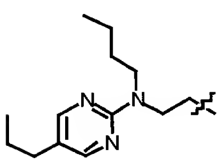

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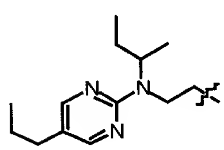

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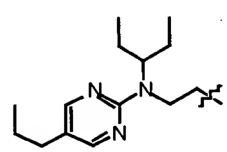


297.

Table 2B cont.

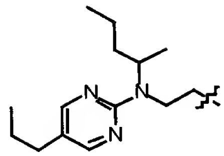
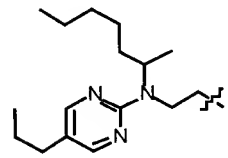
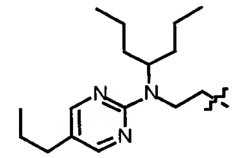
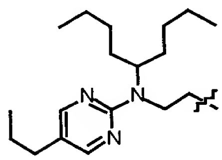
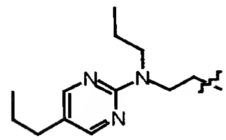
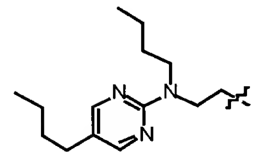
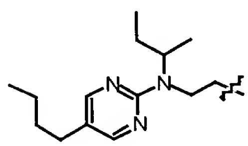
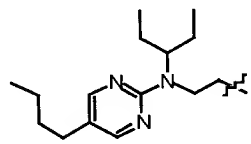
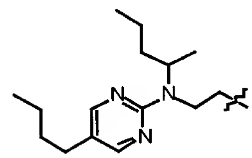
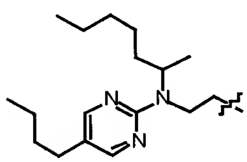
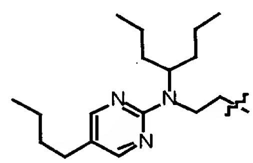
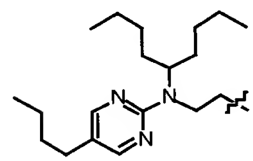
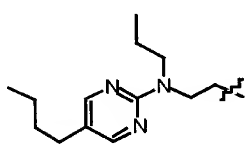
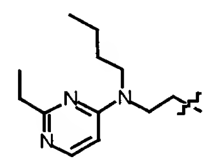
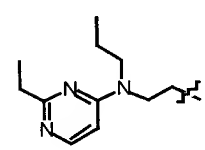
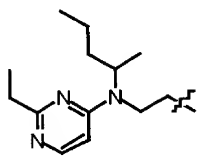
R	R	R
 298.	 299.	 300.
 301.	 302.	 303.
 304.	 305.	 306.
 307.	 308.	 309.
 310.	 311.	 312.

Table 2B cont.

R | **R** | **R**



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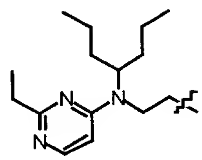

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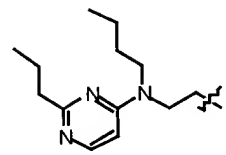

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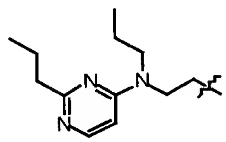

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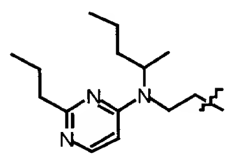

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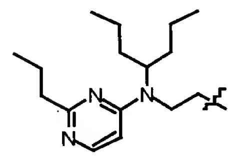

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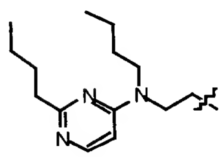

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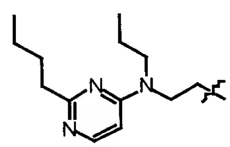

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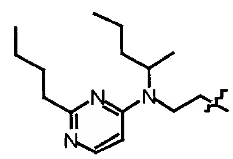

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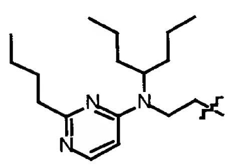

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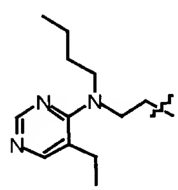

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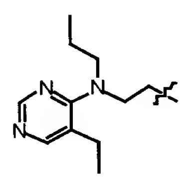

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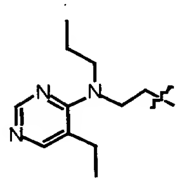

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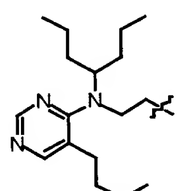

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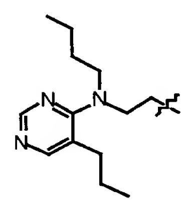

327.

Table 2B cont.

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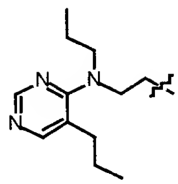
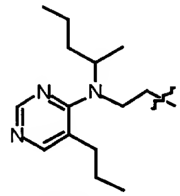
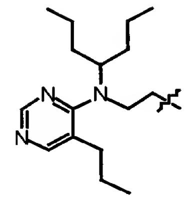
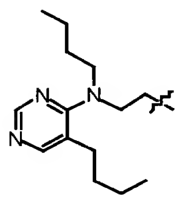
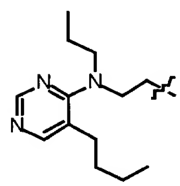
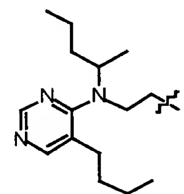
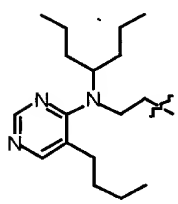
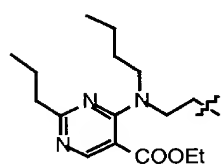
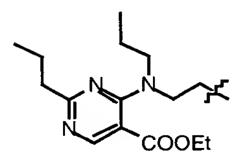
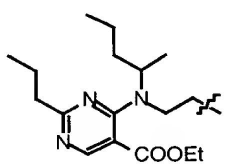
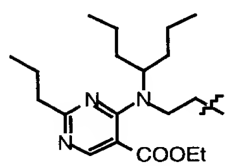
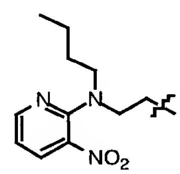
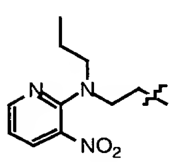
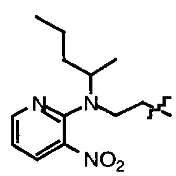
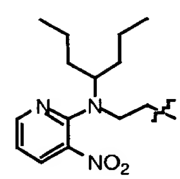
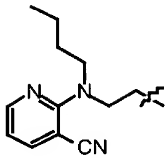
 328.	 329.	 330.
 331.	 332.	 333.
 334.	 335.	 336.
 337.	 338.	 339.
 340.	 341.	 342.

Table 2B cont.

R

R

R



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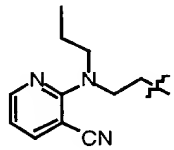

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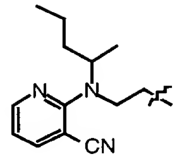

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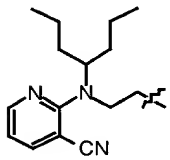

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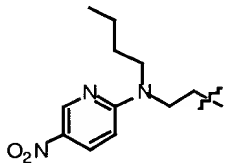

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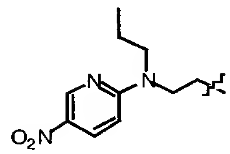

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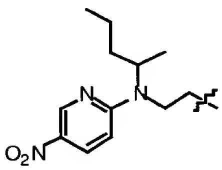

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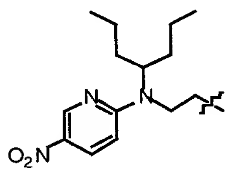

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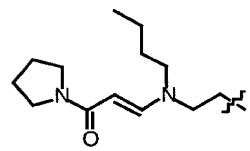

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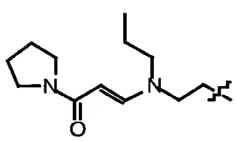

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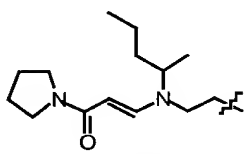

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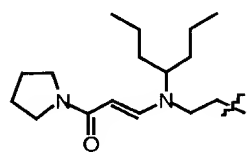

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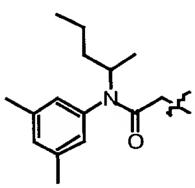

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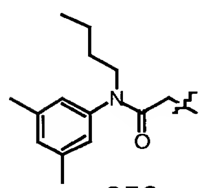

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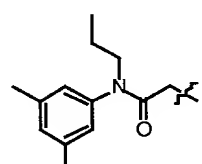

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Table 2B cont.

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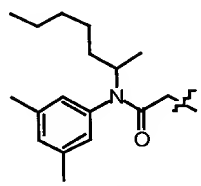
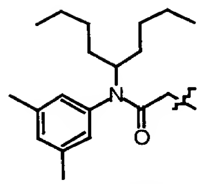
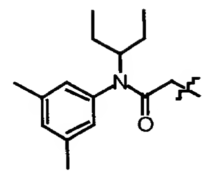
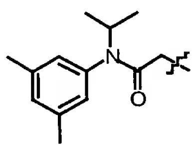
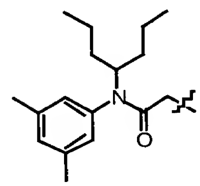
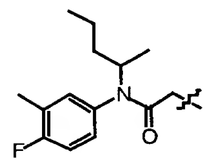
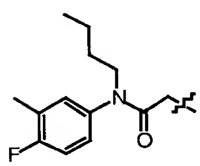
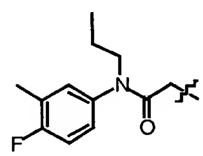
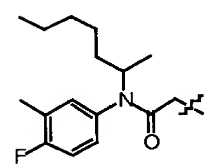
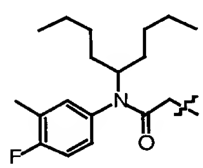
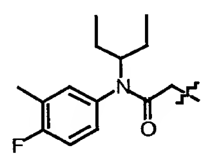
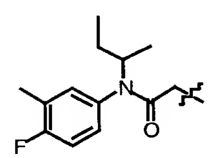
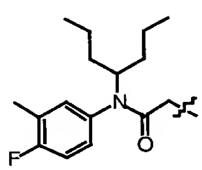
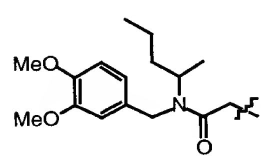
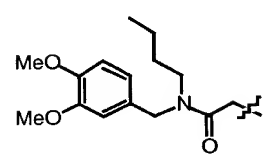
 358.	 359.	 360.
 361.	 362.	 363.
 364.	 365.	 366.
 367.	 368.	 369.
 370.	 371.	 372.

Table 2B cont.

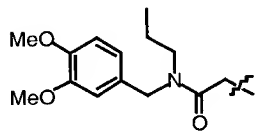
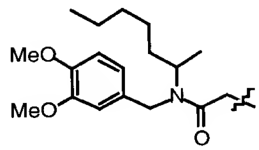
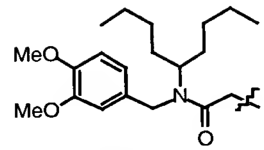
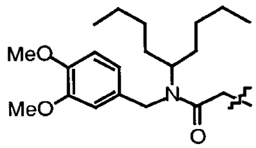
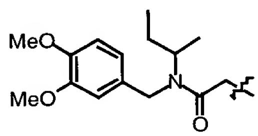
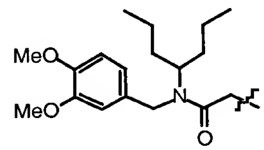
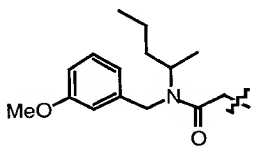
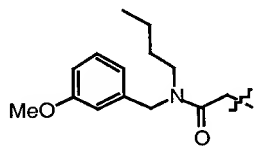
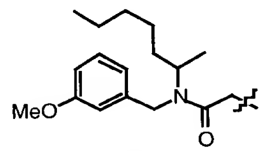
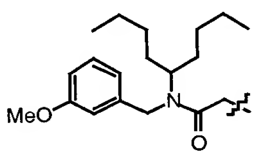
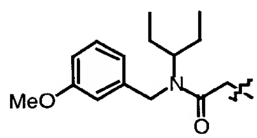
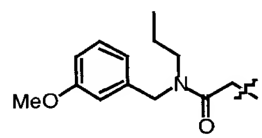
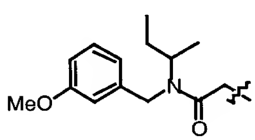
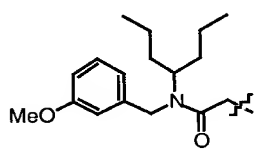
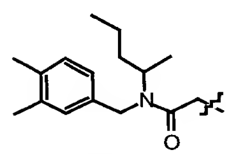
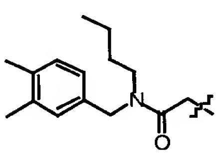
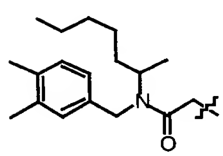
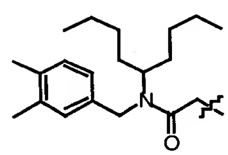
R	R	R
 373.	 374.	 375.
 376.	 377.	 378.
 379.	 380.	 381.
 382.	 383.	 384.
 385.	 386.	 387.
 388.	 389.	 390.

Table 2B cont.

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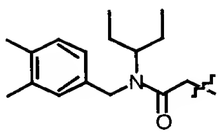
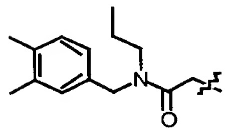
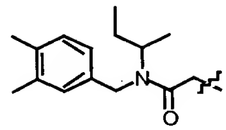
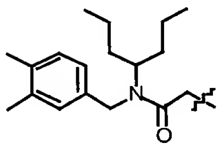
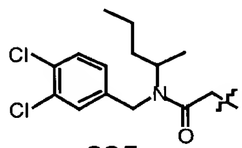
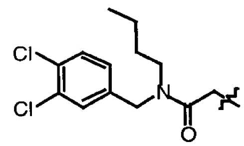
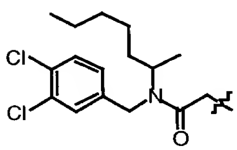
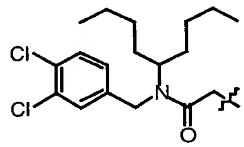
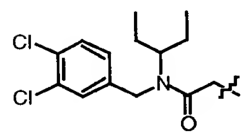
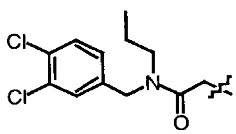
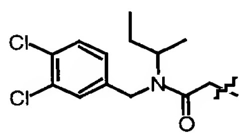
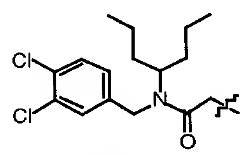
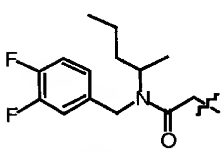
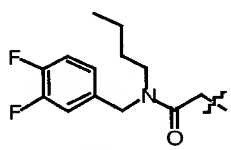
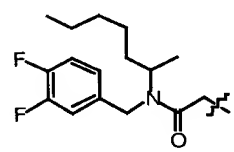
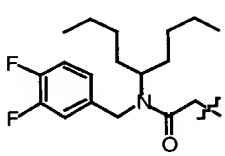
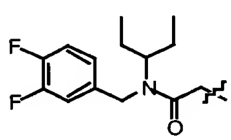
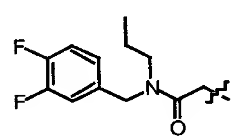
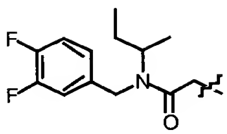
 391.	 392.	 393.
 394.	 395.	 396.
 397.	 398.	 399.
 400.	 401.	 402.
 403.	 404.	 405.
 406.	 407.	 408.

Table 2B cont.

R	R	R



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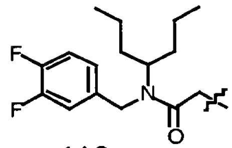

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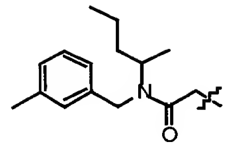

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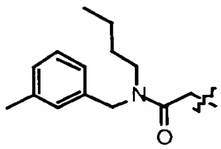

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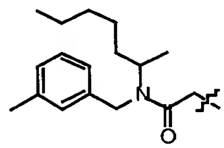

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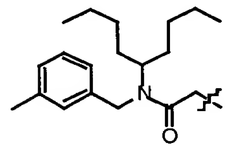

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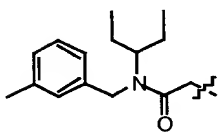

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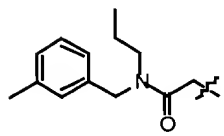

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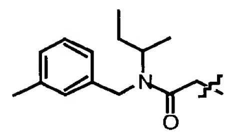

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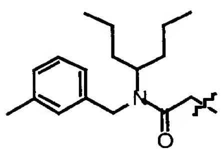

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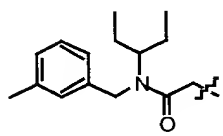

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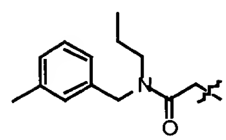

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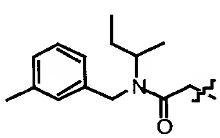

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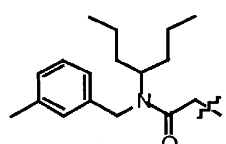

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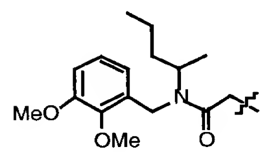

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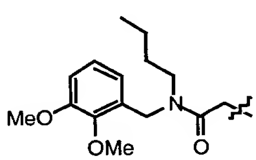

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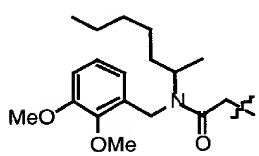

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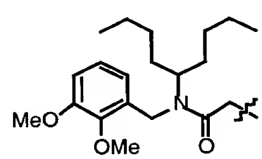
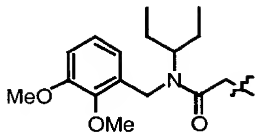


426.

Table 2B cont.

R **R** **R**



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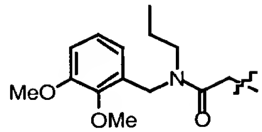

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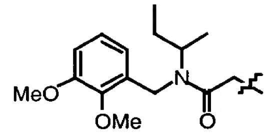

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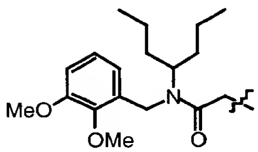

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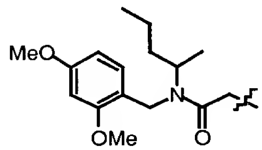

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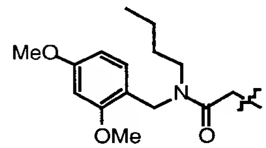

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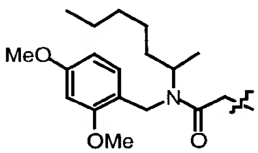

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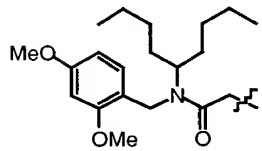

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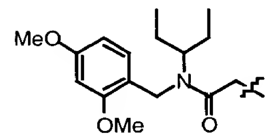

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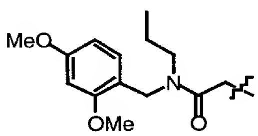

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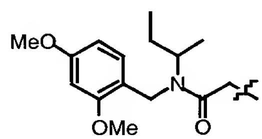

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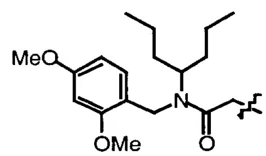

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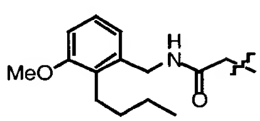

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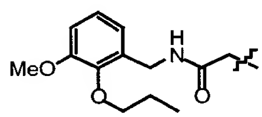

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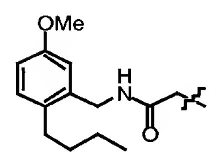

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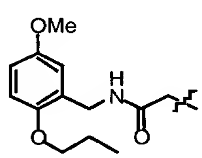

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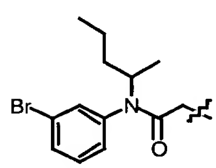

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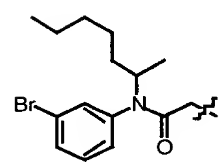


444.

Table 2B cont.

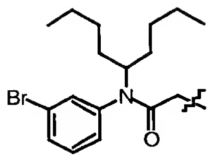
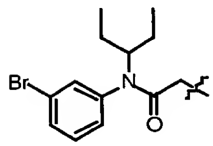
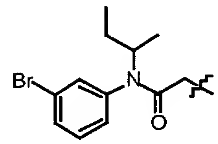
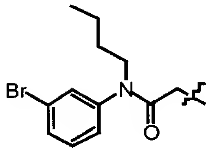
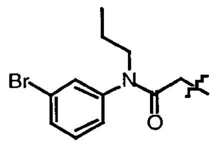
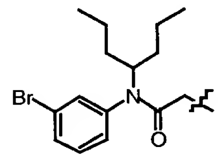
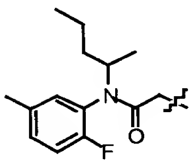
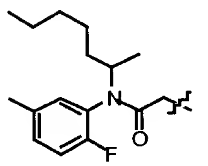
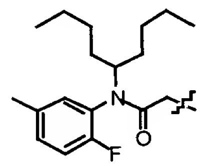
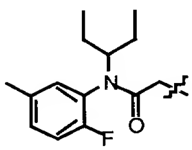
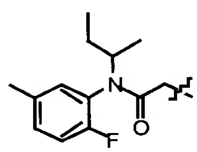
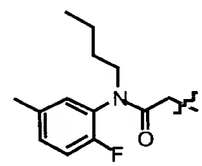
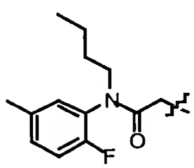
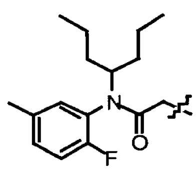
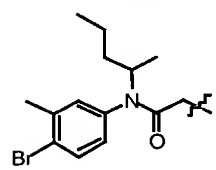
R	R	R
 445.	 446.	 447.
 448.	 449.	 450.
 451.	 452.	 453.
 454.	 455.	 456.
 457.	 458.	 459.

Table 2B cont.

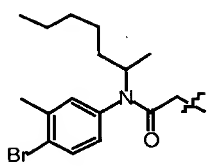
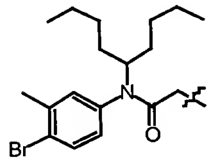
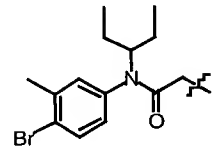
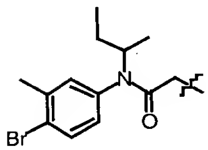
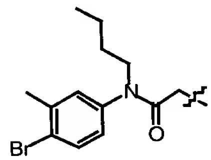
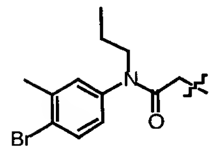
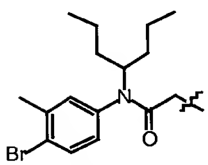
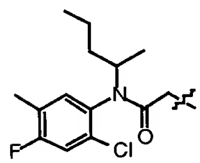
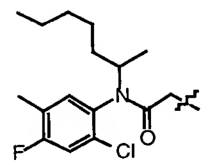
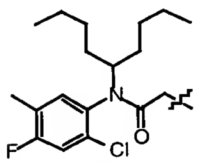
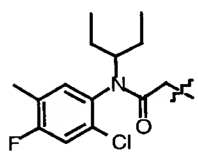
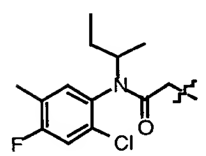
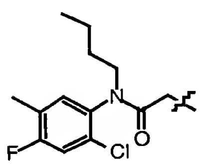
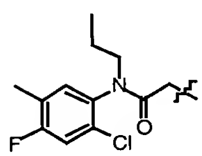
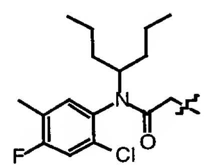
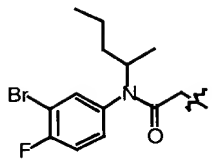
R	R	R
 460.	 461.	 462.
 463.	 464.	 465.
 466.	 467.	 468.
 469.	 470.	 471.
 472.	 473.	 474.

Table 2B cont.

R **R** **R**



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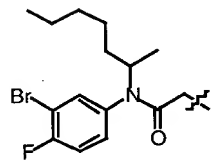

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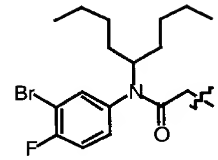

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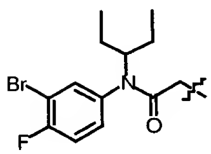

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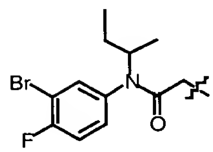

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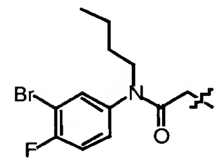

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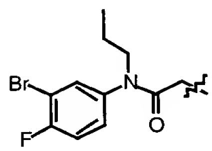

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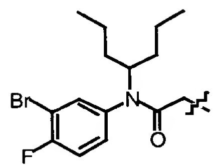

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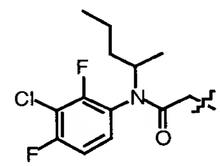

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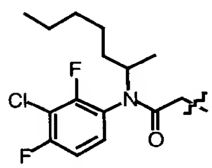

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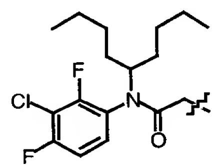

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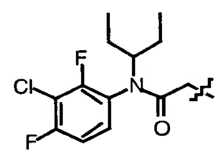

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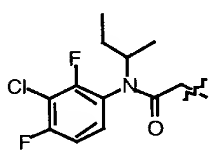

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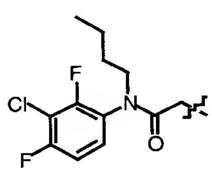

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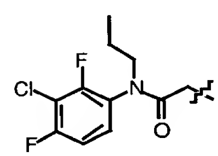

489.

Table 2B cont.

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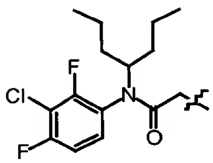
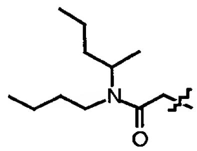
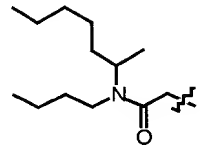
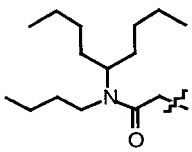
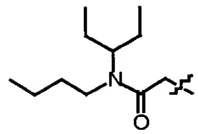
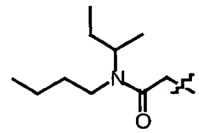
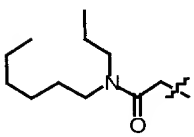
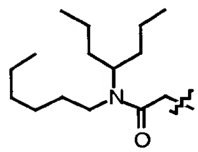
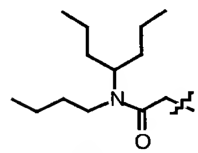
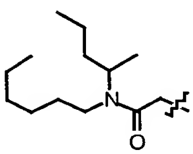
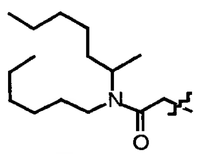
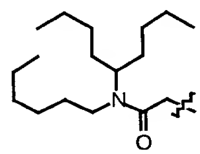
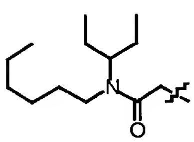
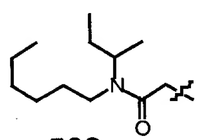
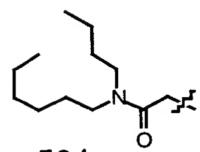
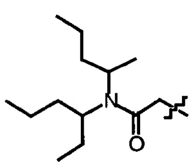
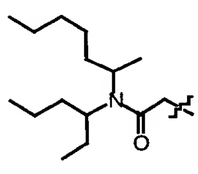
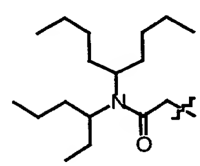
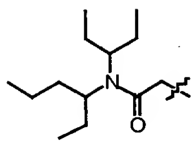
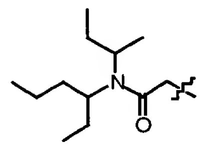
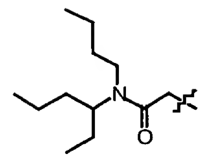
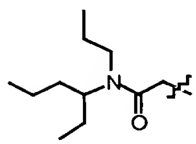
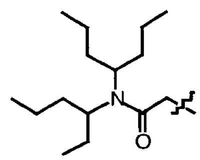
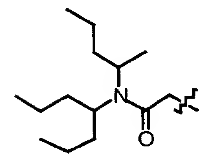
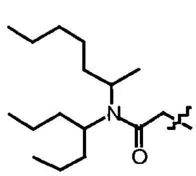
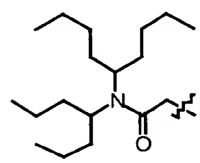
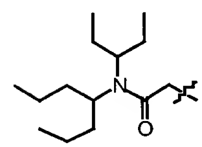
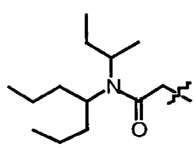
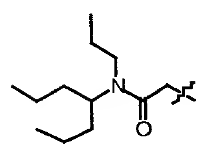
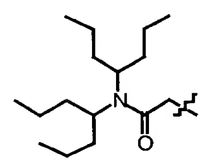
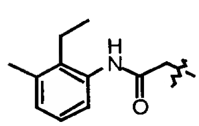
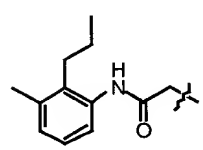
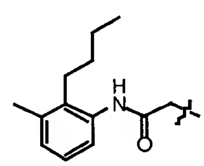
 490.	 491.	 492.
 493.	 494.	 495.
 496.	 497.	 498.
 499.	 500.	 501.
 502.	 503.	 504.
 505.	 506.	 507.

Table 2B cont.

R	R	R
 508.	 509.	 510.
 511.	 512.	 513.
 514.	 515,	 516.
 517.	 518.	 519.
 520.	 521.	 522.

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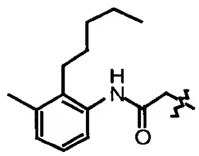

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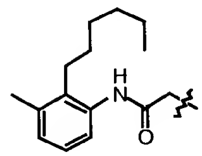

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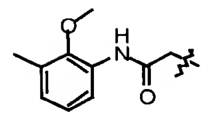

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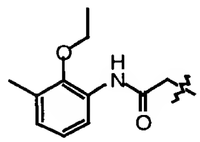

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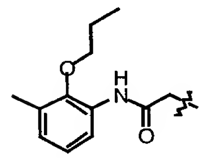

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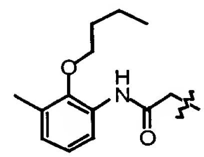

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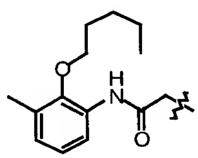

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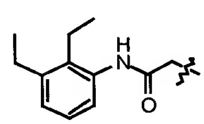

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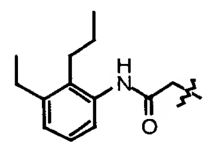

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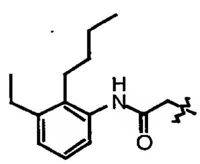

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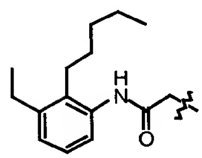

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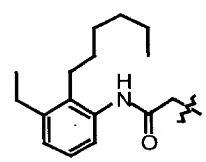

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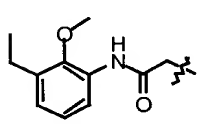

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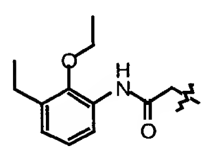

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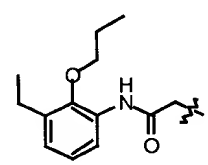

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Table 2B cont.

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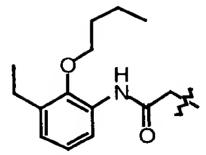
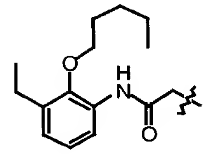
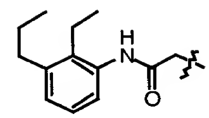
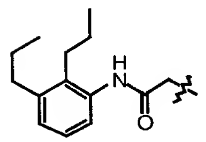
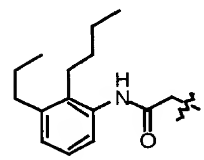
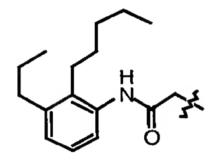
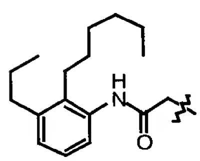
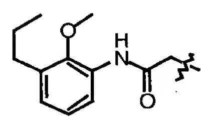
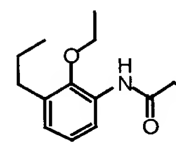
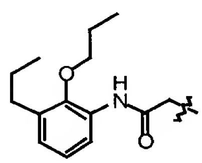
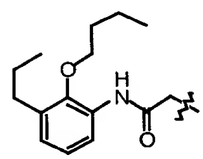
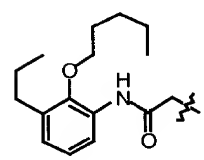
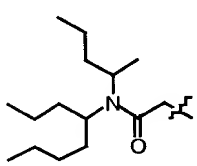
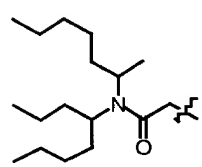
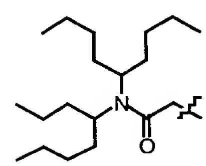
 538.	 539.	 540.
 541.	 542.	 543.
 544.	 545.	 546.
 547.	 548.	 549.
 550.	 551.	 552.

Table 2B cont.

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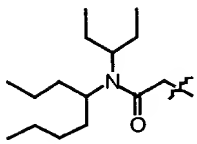
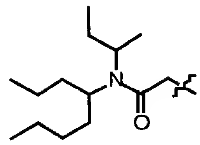
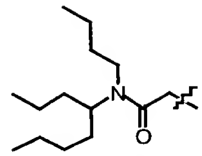
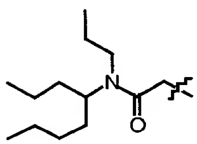
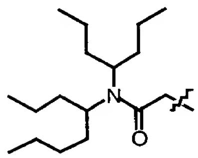
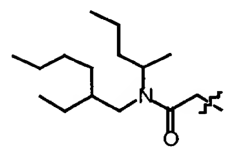
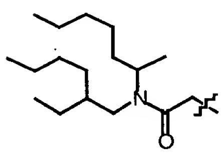
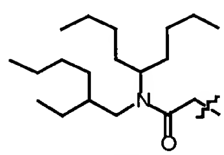
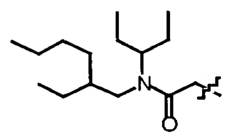
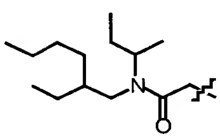
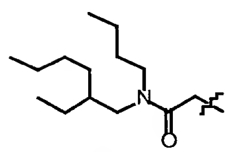
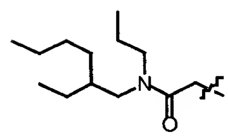
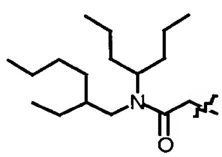
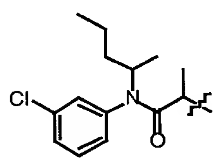
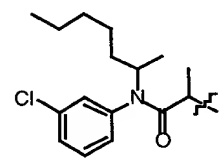
 553.	 554.	 555.
 556.	 557.	 558.
 559.	 560.	 561.
 562.	 563.	 564.
 565.	 566.	 567.

Table 2B cont.

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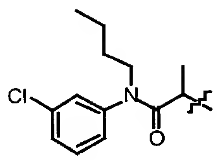
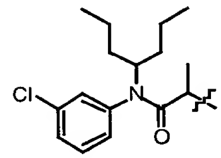
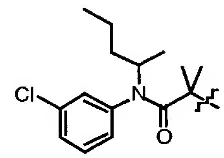
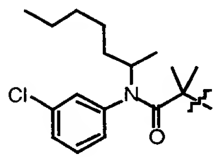
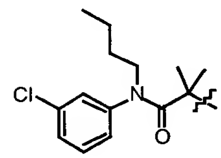
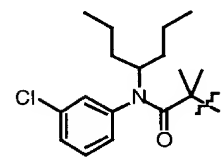
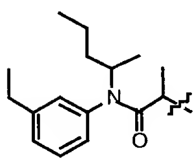
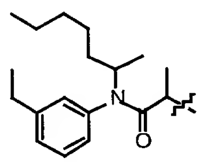
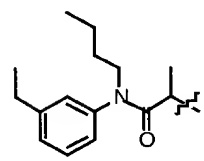
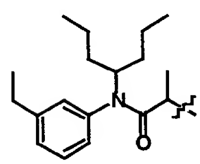
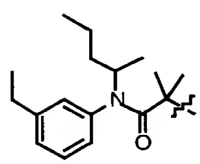
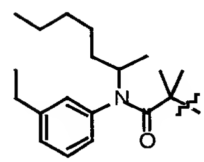
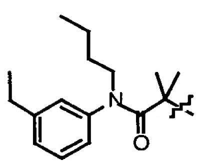
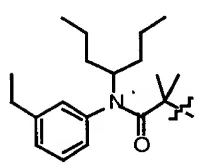
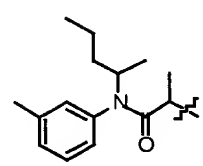
 568.	 569.	 570.
 571.	 572.	 573.
 574.	 575.	 576.
 577.	 578.	 579.
 580.	 581.	 582.

Table 2B cont.

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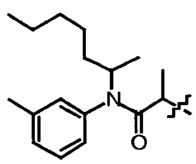
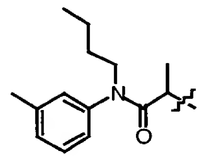
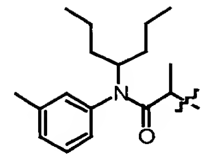
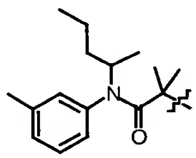
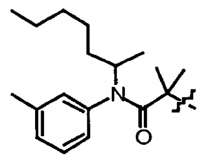
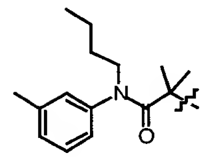
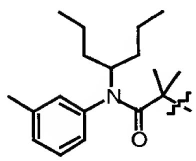
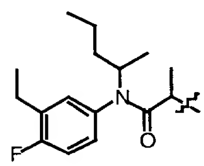
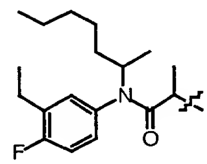
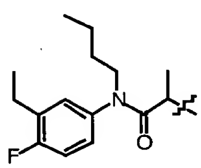
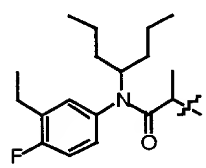
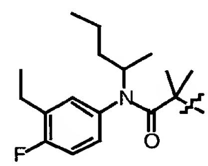
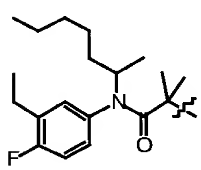
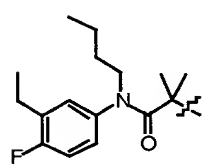
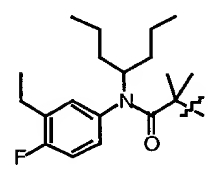
 583.	 584.	 585.
 586.	 587.	 588.
 589.	 590.	 591.
 592.	 593.	 594.
 595.	 596.	 597.

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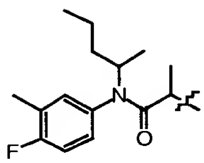
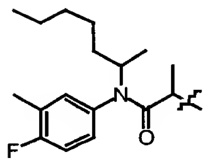
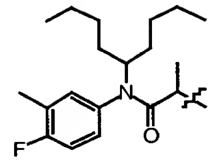
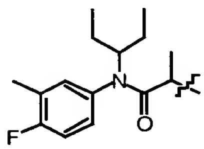
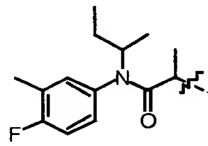
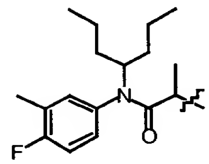
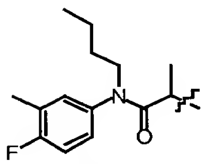
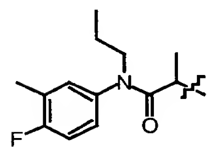
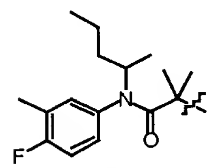
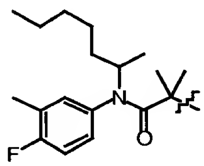
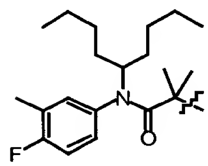
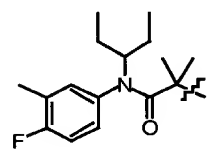
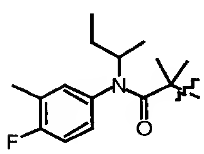
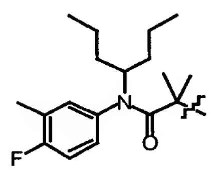
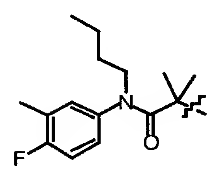
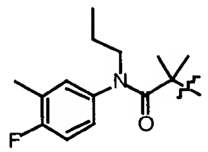
R	R	R
 598.	 599.	 600.
 601.	 602.	 603.
 604.	 605.	 606.
 607.	 608.	 609.
 610.	 611.	 612.

Table 2B cont.

R | R | R



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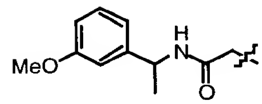

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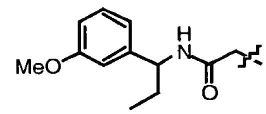

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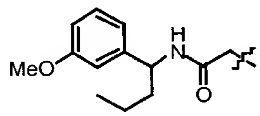

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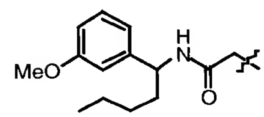

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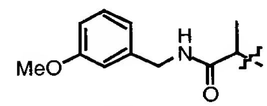

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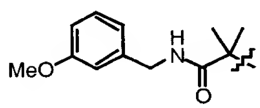

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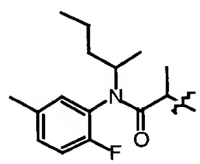

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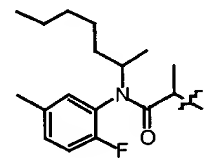

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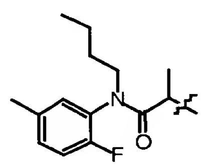

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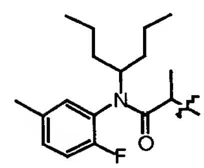

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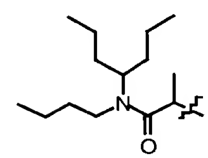

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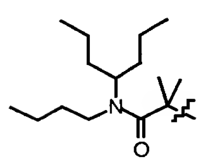

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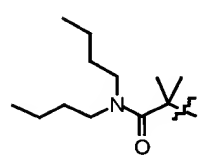

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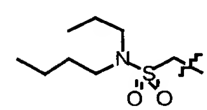

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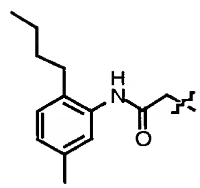
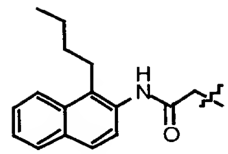
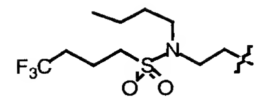
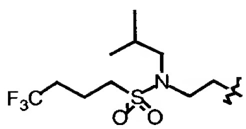
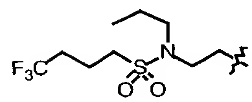
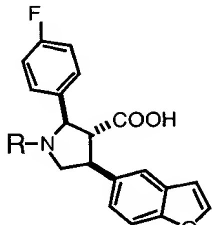
Table 2B cont.

R	R	R
		
628.	629.	630.
		
631.	632.	

<u>Example 339</u>

Using methods described in the above examples, compounds comprising a parent structure selected from those disclosed in Table 3A and an R substituent selected from those disclosed in Table 3B can be prepared.

Table 3A



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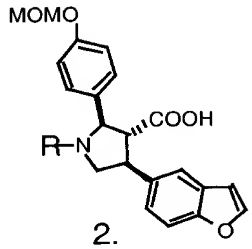

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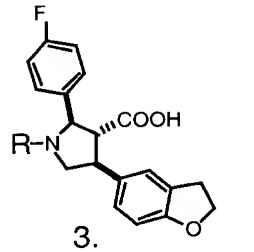

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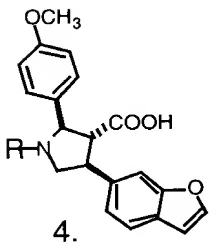

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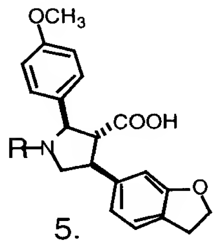

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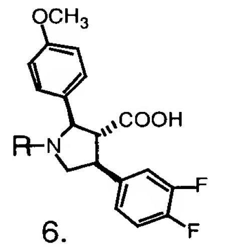

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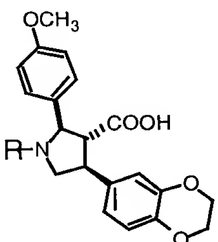

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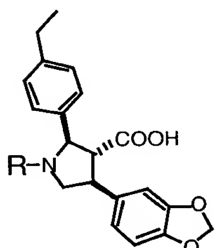

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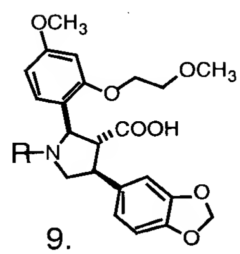

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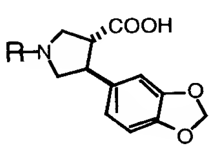

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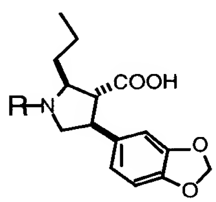

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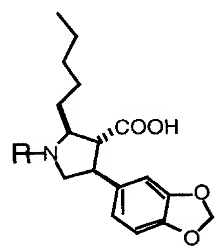
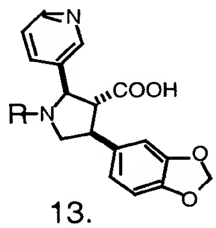


12.

Table 3A cont.



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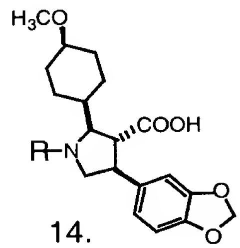

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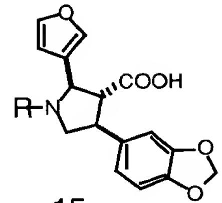

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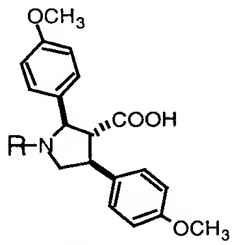

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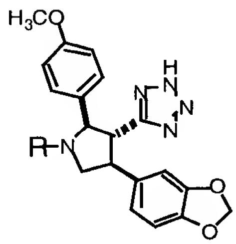

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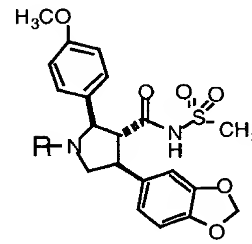

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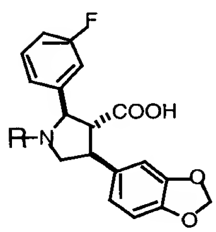

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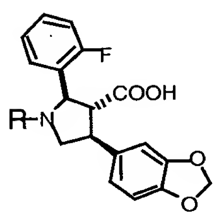

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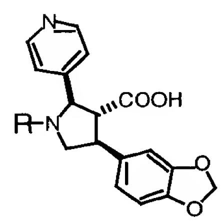
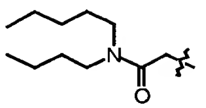


21.

Table 3B

R	R	R



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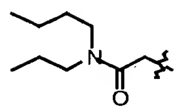

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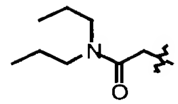

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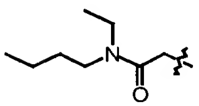
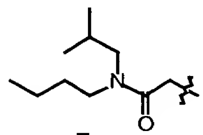


4.



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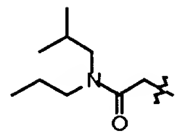

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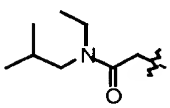

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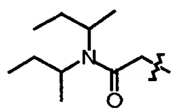

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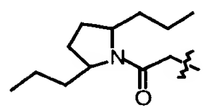

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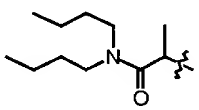

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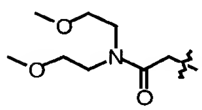

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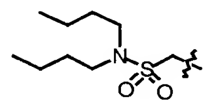

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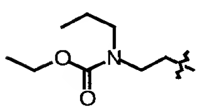

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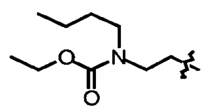

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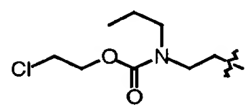

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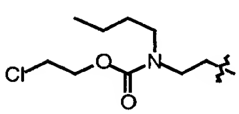

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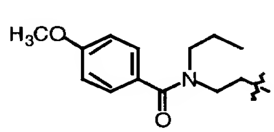

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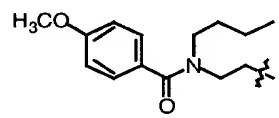

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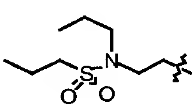

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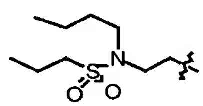

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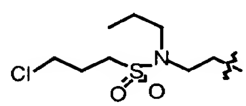

21.

Table 3B cont.

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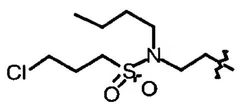
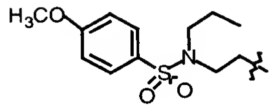
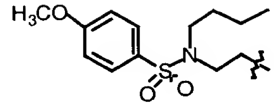
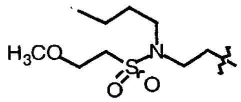
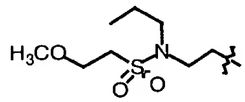
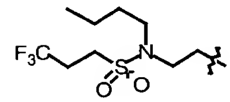
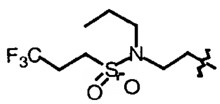
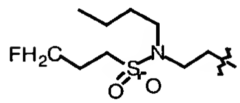
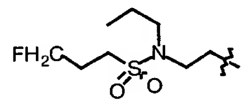
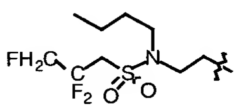
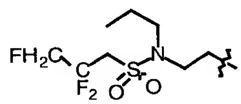
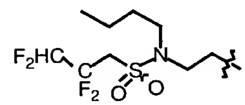
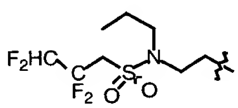
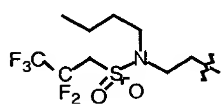
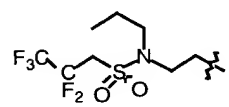
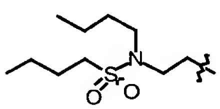
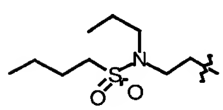
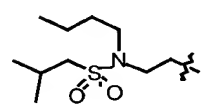
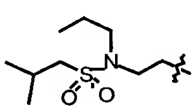
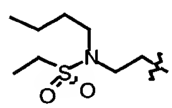
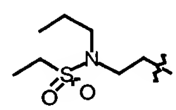
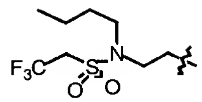
 22.	 23.	 24.
 25.	 26.	 27.
 28.	 29.	 30.
 31.	 32.	 33.
 34.	 35.	 36.
 37.	 38.	 39.
 40.	 41.	 42.

Table 3B cont.

R **R** **R**



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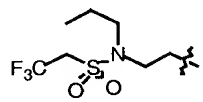

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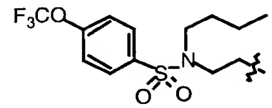

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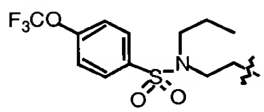

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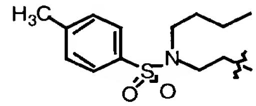

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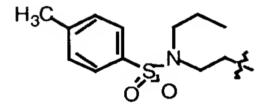

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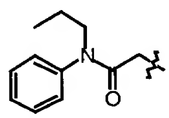

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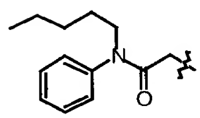

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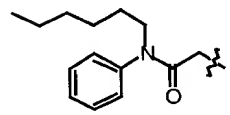

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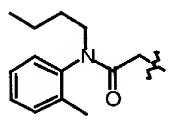

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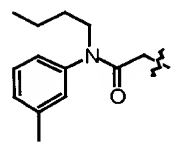

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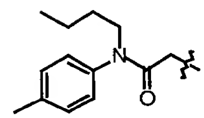

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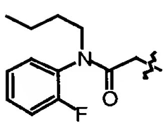

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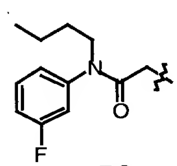

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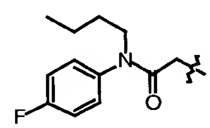

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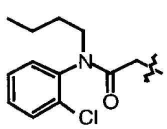

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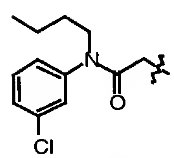

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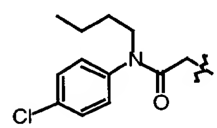

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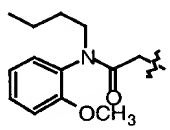
Table 3B cont.

R **R** **R**



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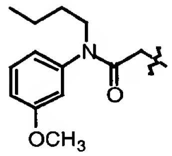

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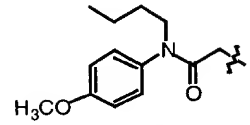

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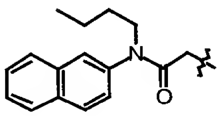

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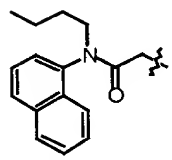

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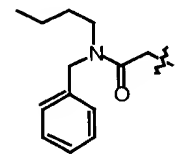

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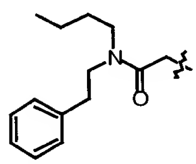

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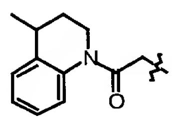

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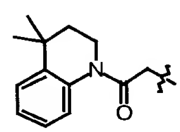

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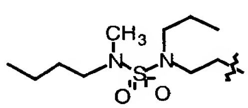

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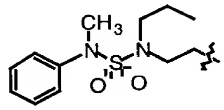

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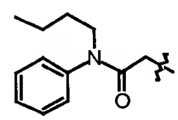

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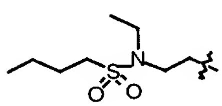

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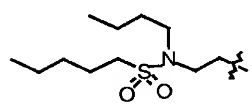

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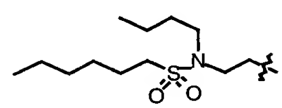

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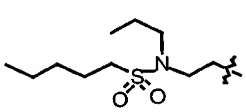

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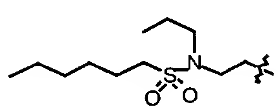

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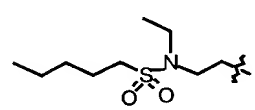


78.

Table 3B cont.

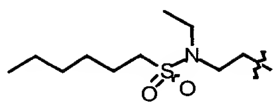
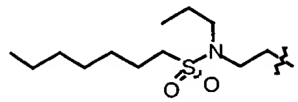
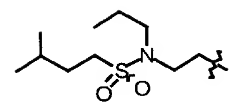
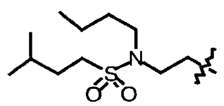
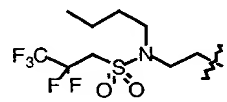
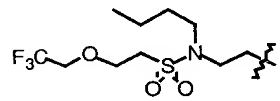
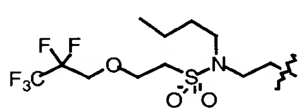
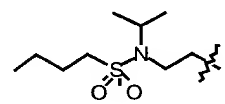
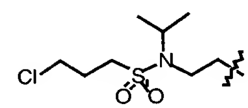
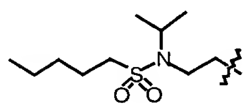
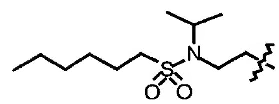
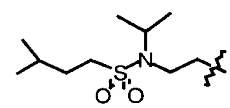
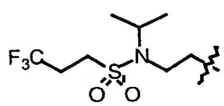
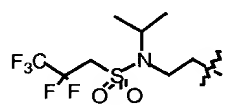
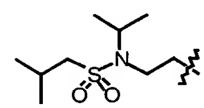
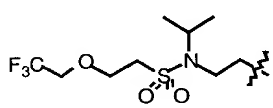
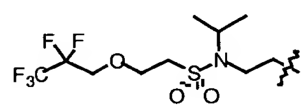
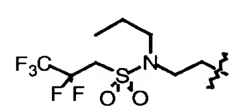
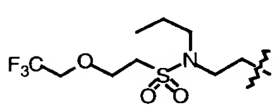
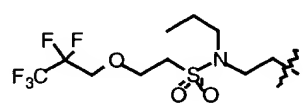
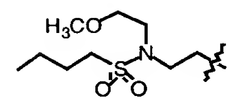
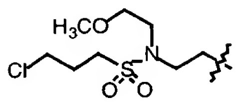
R	R	R
 79.	 80.	 81.
 82.	 83.	 84.
 85.	 86.	 87.
 88.	 89.	 90.
 91.	 92.	 93.
 94.	 95.	 96.
 97.	 98.	 99.

Table 3B cont.

R **R** **R**



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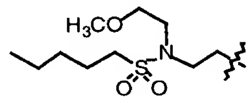

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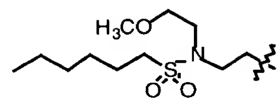

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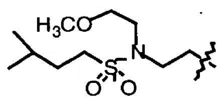

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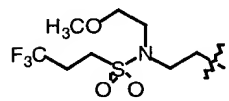

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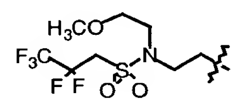

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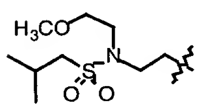

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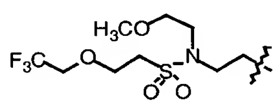

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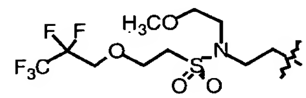

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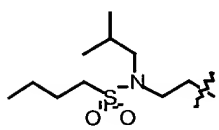

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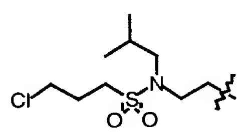

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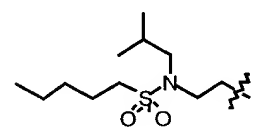

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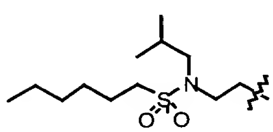

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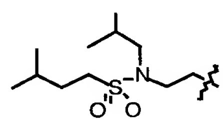

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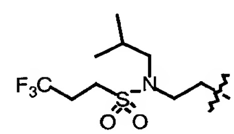

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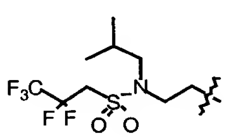

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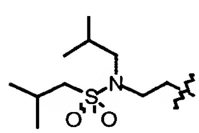

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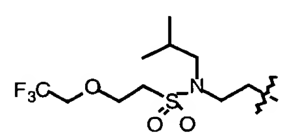
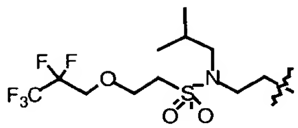


117.

Table 3B cont.

R **R** **R**



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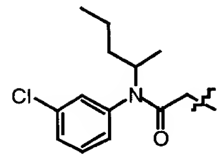

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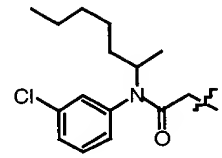

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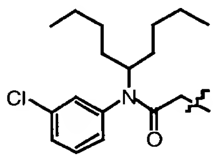

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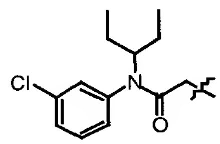

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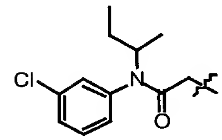

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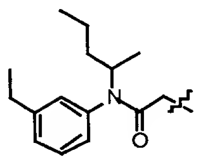

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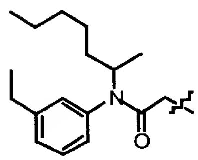

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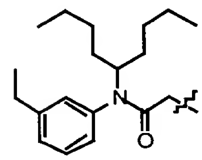

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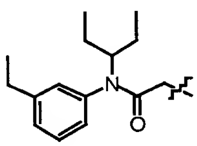

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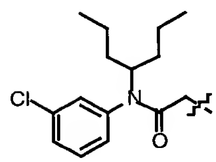

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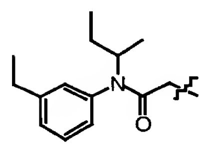

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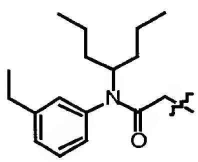

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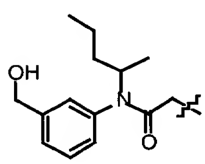

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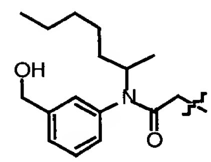
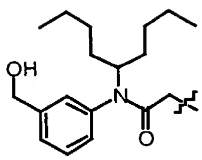


132.

Table 3B cont.

R R R



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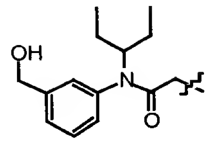

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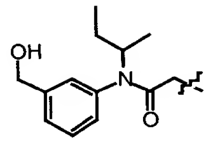

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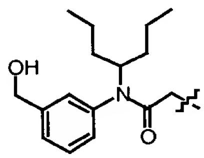

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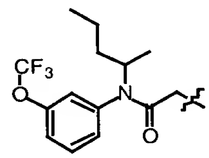

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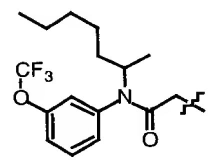

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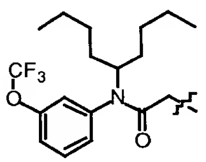

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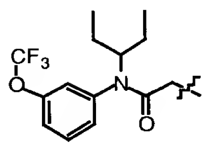

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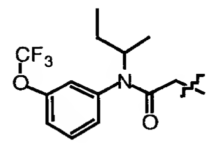

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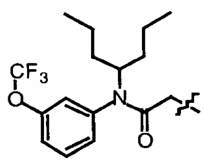

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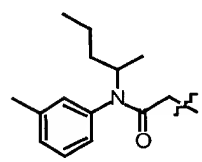

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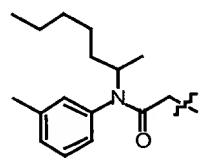

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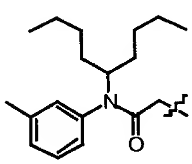

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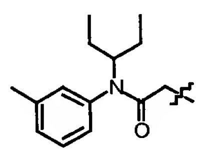

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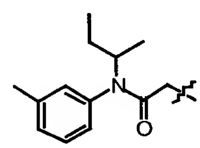
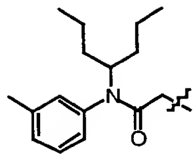


147.

Table 3B cont.

R	R	R



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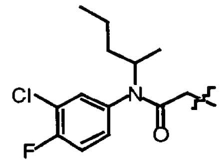

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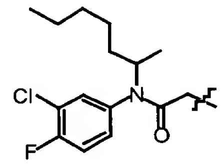

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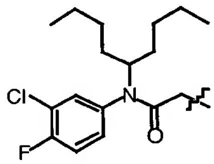

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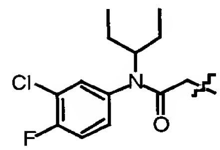
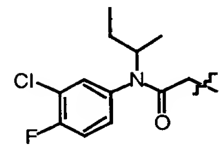
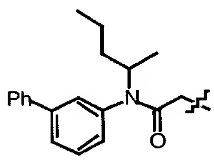


152.



153.



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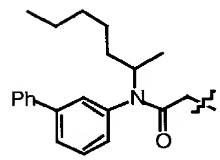

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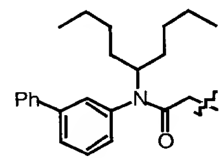

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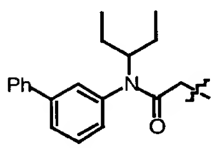

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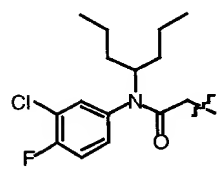

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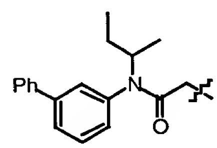

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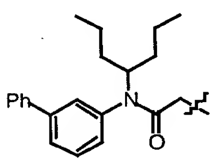

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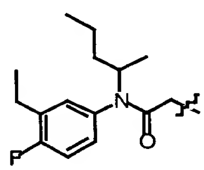

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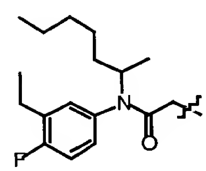
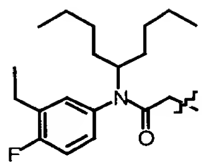


162.

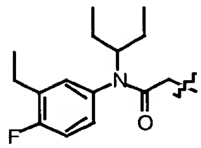
Table 3B cont.

R



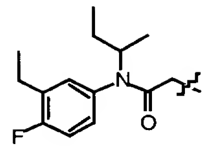
163.

R



164.

R



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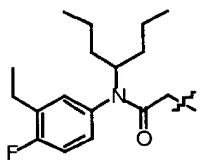

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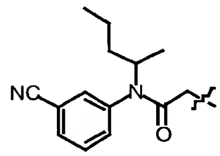

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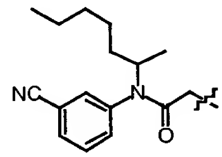

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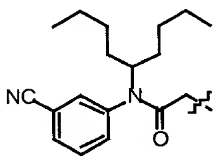

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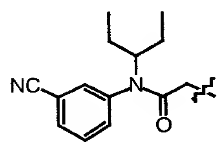

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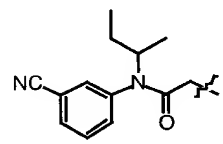

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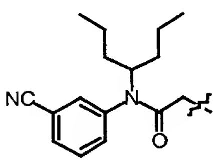

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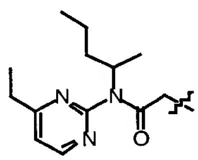

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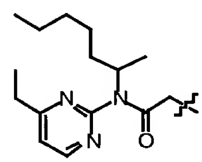

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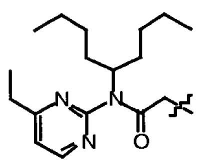

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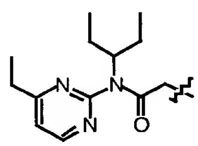

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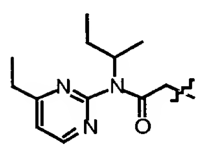

177.

Table 3B cont.

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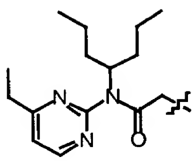
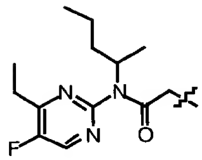
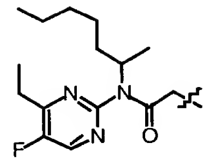
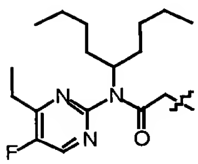
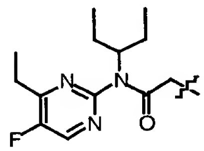
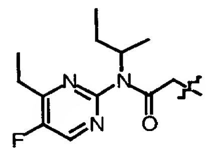
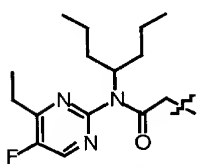
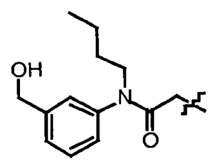
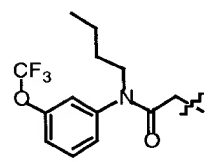
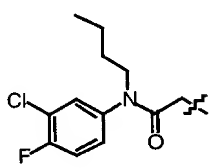
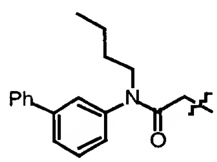
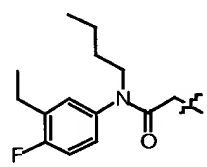
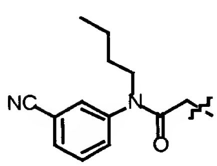
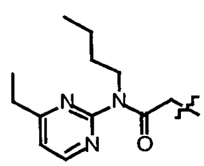
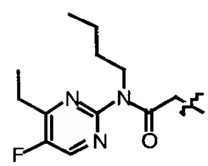
 178.	 179.	 180.
 181.	 182.	 183.
 184.	 185.	 186.
 187.	 188.	 189.
 190.	 191.	 192.

Table 3B cont.

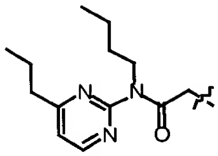
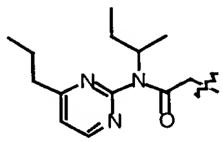
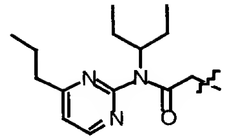
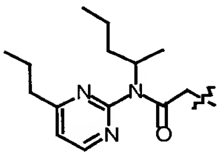
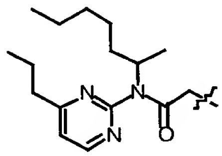
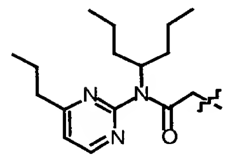
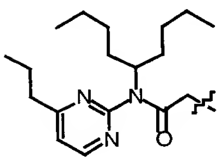
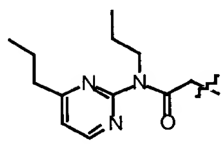
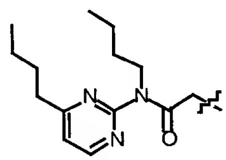
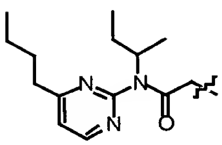
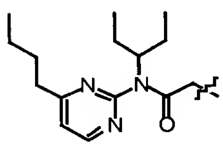
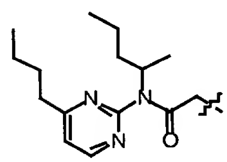
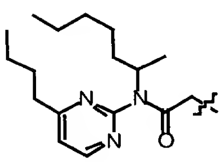
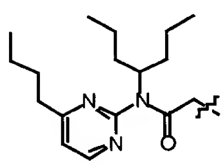
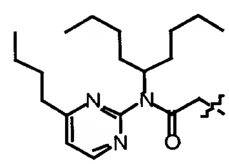
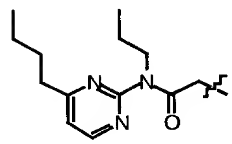
R	R	R
 193.	 194.	 195.
 196.	 197.	 198.
 199.	 200.	 201.
 202.	 203.	 204.
 205.	 206.	 207.

Table 3B cont.

R	R	R



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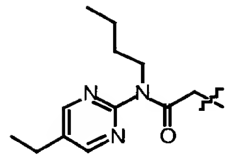

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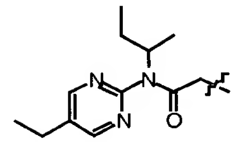

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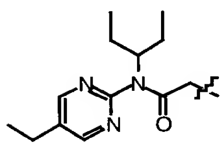

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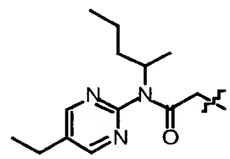

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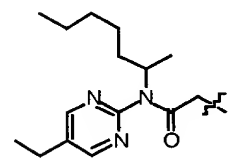

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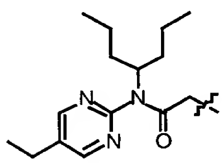

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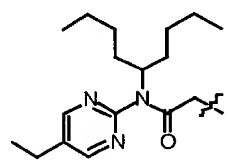

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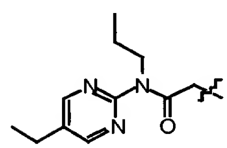

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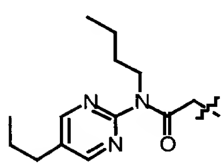

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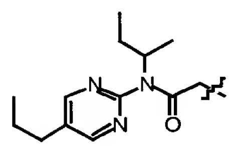
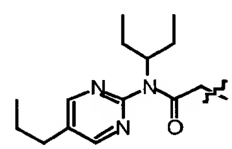
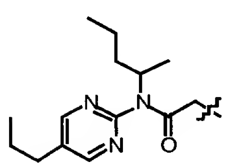


218.



219.



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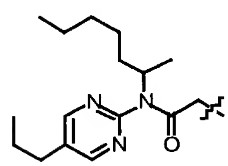

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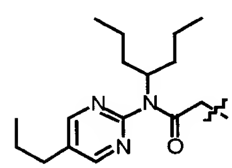
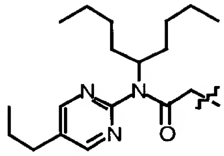


222.

Table 3B cont.

R | R | R



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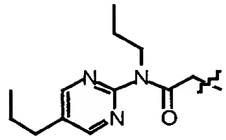
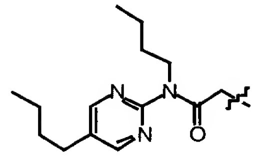
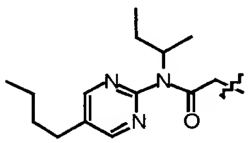


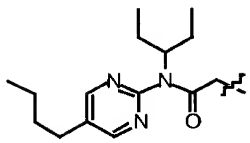
224.



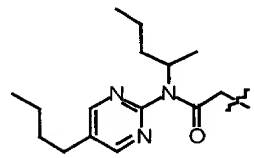
225.



226.



227.



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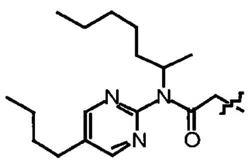

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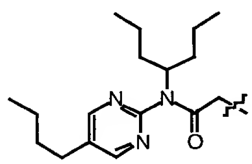

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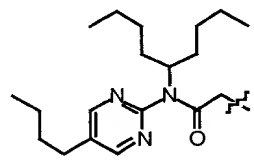

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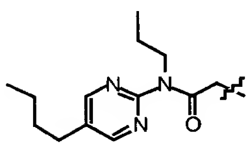

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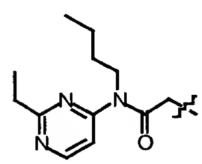

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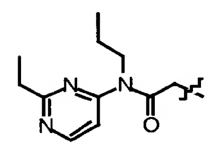

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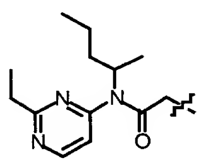

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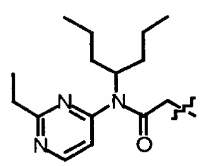

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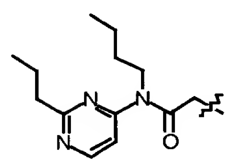

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Table 3B cont.

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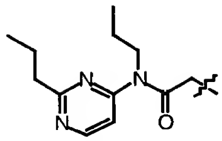
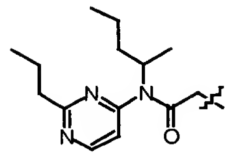
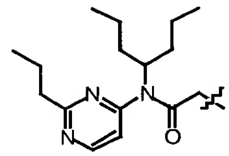
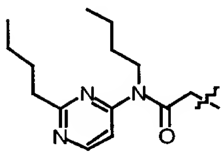
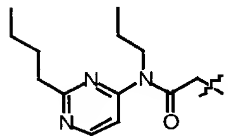
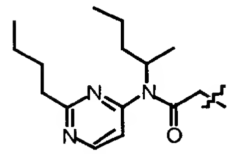
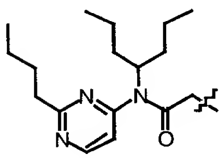
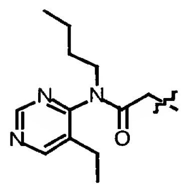
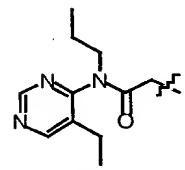
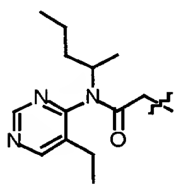
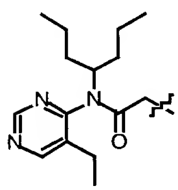
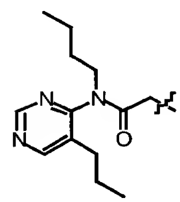
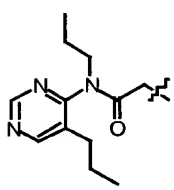
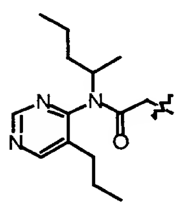
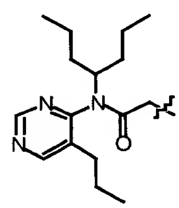
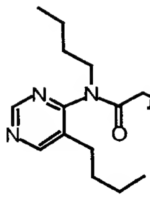
 238.	 239.	 240.
 241.	 242.	 243.
 244.	 245.	 246.
 247.	 248.	 249.
 250.	 252.	 252.

Table 3B cont.

R **R** **R**



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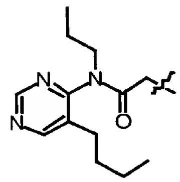
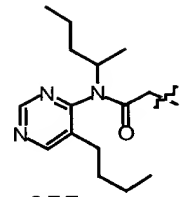


254.



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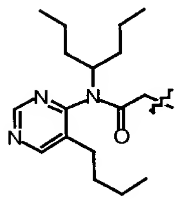
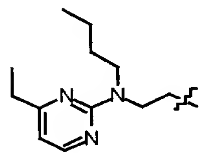


256.



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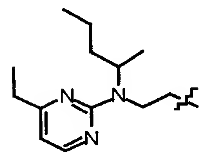

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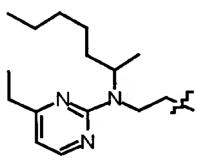

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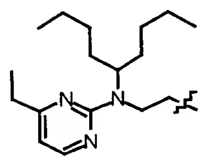

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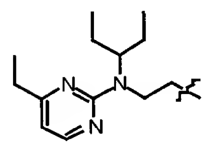

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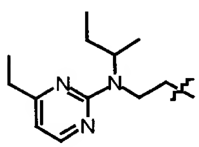

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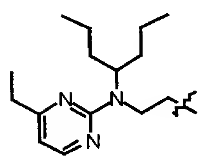
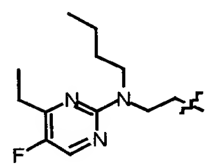


263.



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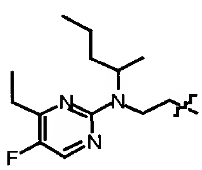

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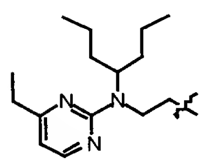

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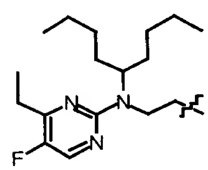


267.

Table 3B cont.

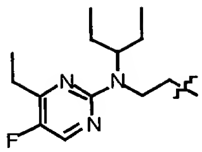
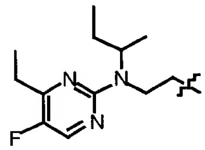
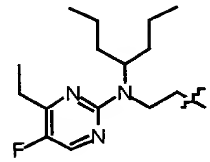
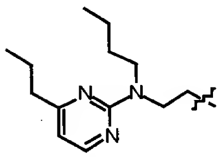
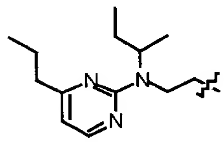
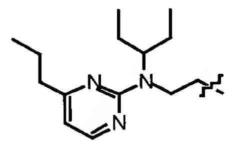
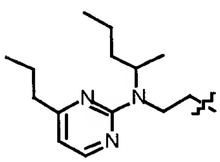
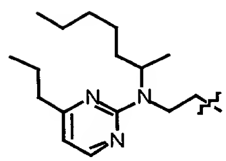
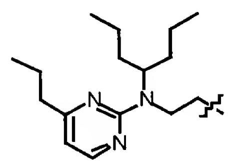
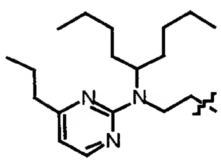
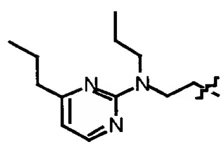
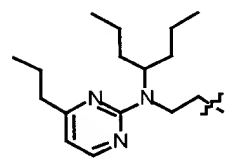
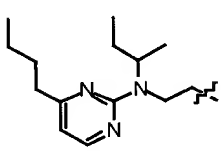
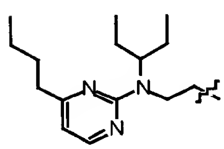
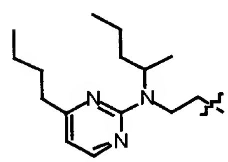
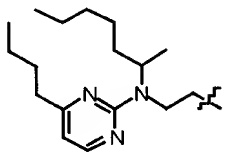
R	R	R
 268.	 269.	 270.
 271.	 272.	 273.
 274.	 275.	 276.
 277.	 278.	 279.
 280.	 281.	 282.

Table 3B cont.

R **R** **R**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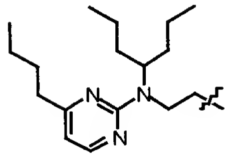
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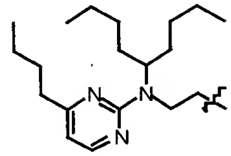
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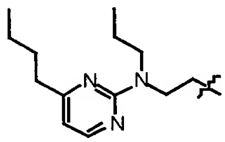
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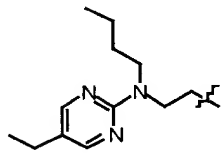
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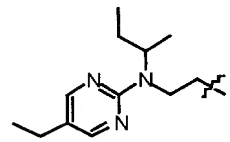
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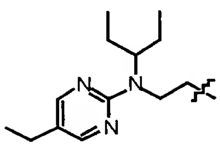
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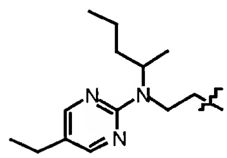
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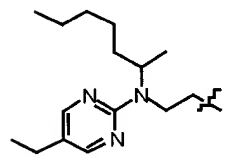
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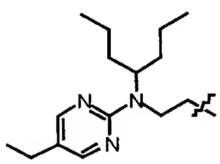
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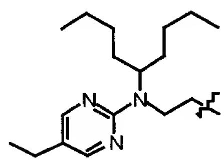
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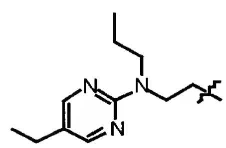
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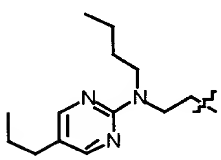
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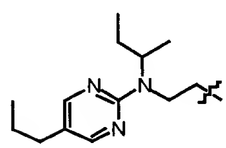
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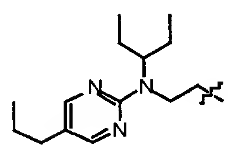
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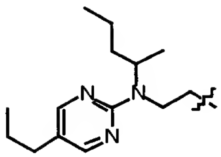
Table 3B cont.

R R R



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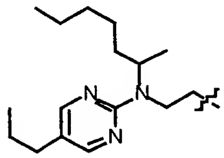
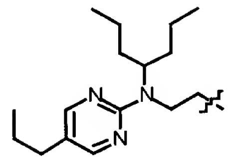
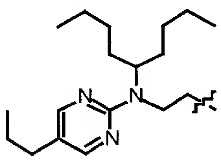


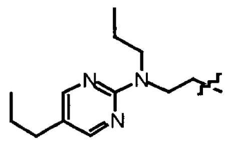
299.



300.



301.



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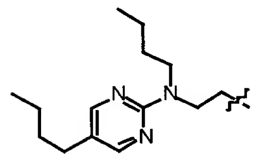

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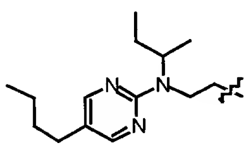

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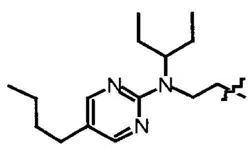

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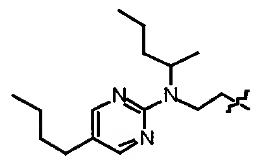

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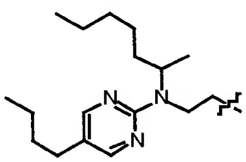

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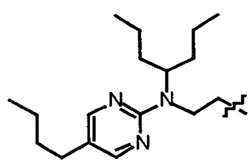

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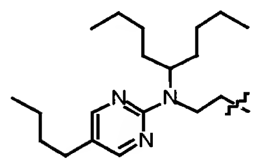

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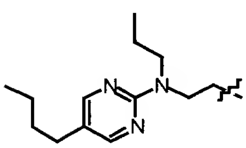

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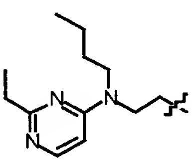

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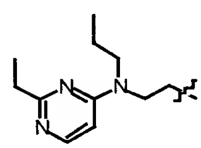

312.

Table 3B cont.

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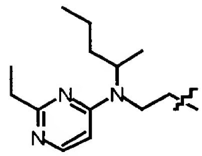
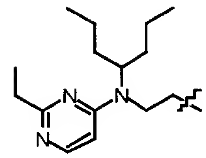
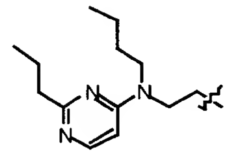
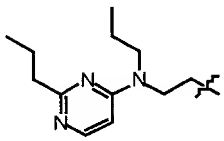
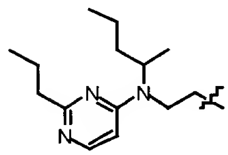
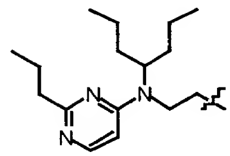
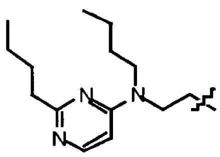
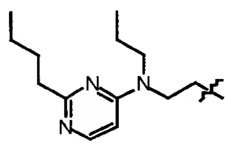
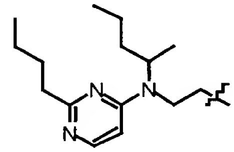
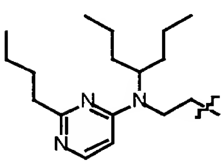
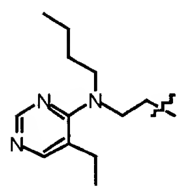
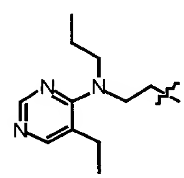
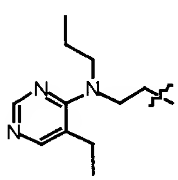
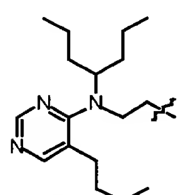
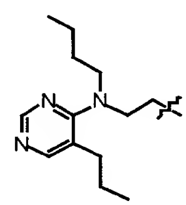
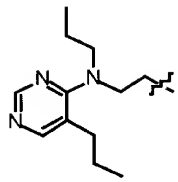
 313.	 314.	 315.
 316.	 317.	 318.
 319.	 320.	 321.
 322.	 323.	 324.
 325.	 326.	 327.

Table 3B cont.

R **R** **R**



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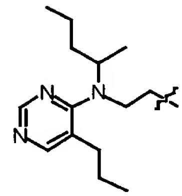

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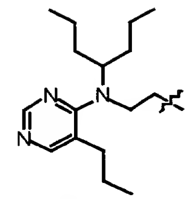

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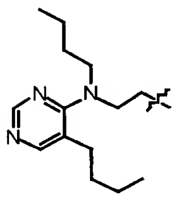

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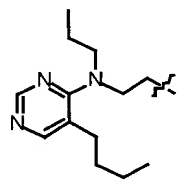

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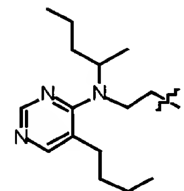

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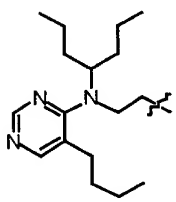

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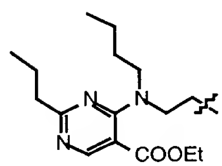

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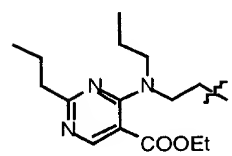

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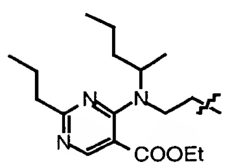

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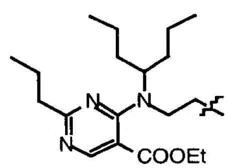

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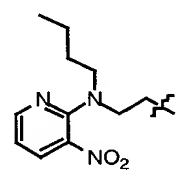

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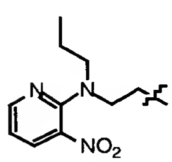

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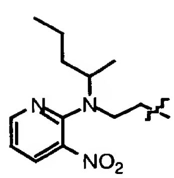

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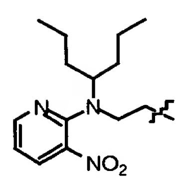

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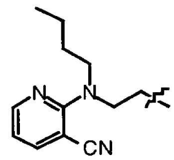
Table 3B cont.

R **R** **R**



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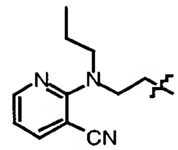

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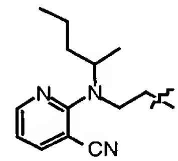

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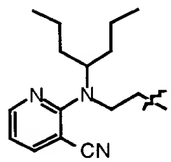

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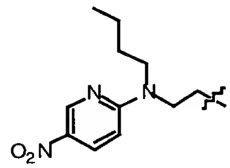

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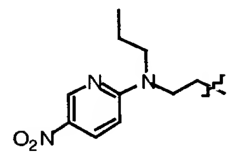

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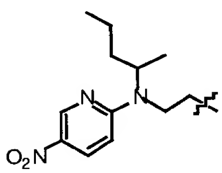

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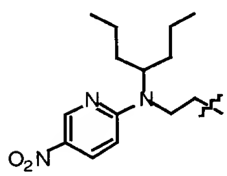

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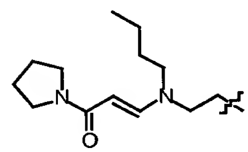

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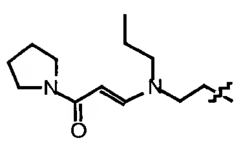

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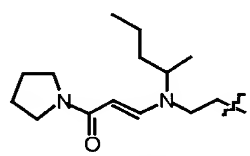

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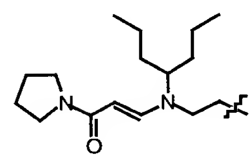

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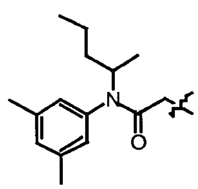

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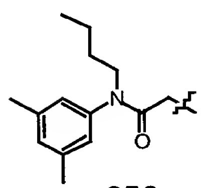

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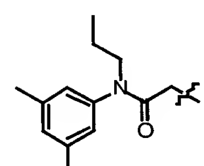


357.

Table 3B cont.

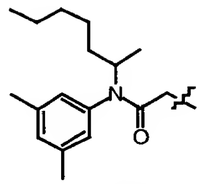
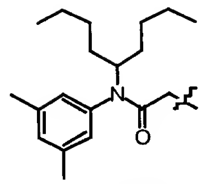
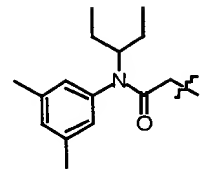
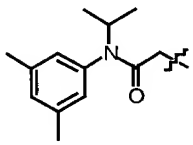
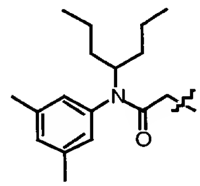
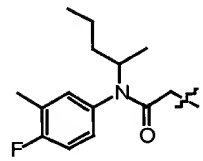
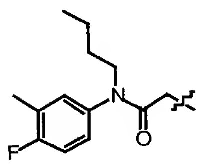
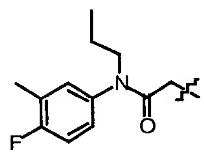
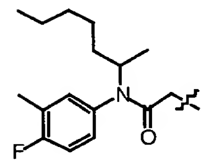
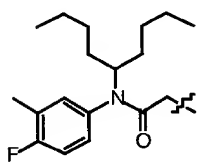
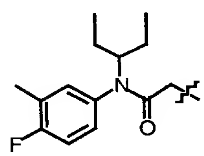
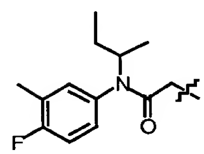
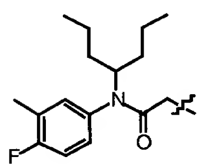
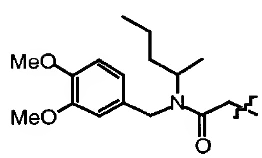
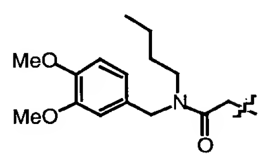
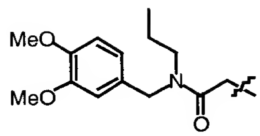
R	R	R
 358.	 359.	 360.
 361.	 362.	 363.
 364.	 365.	 366.
 367.	 368.	 369.
 370.	 371.	 372.

Table 3B cont.

R	R	R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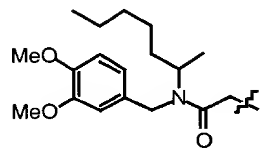
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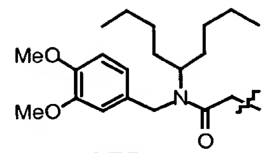
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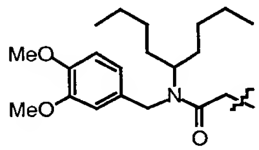
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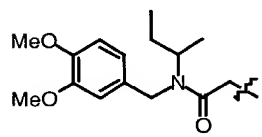
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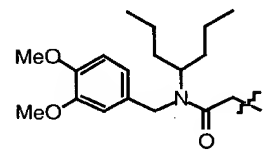
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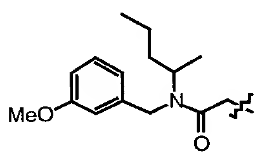
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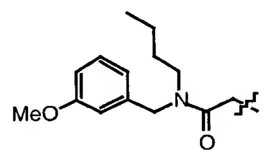
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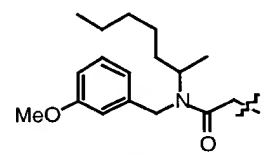
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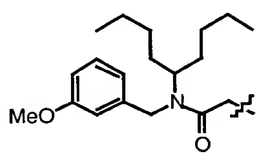
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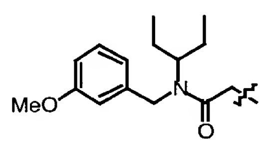
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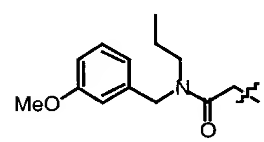
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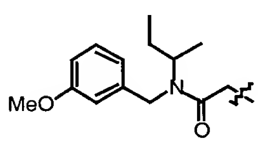
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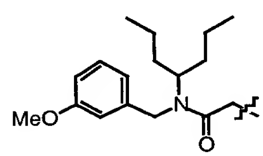
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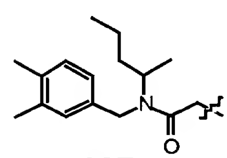
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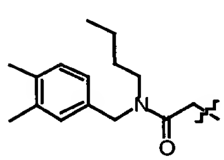
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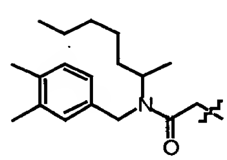
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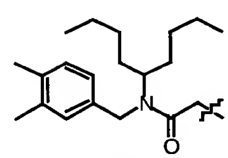
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Table 3B cont.

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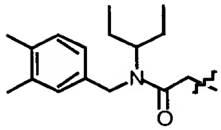
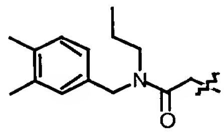
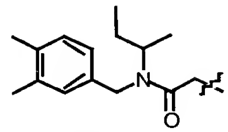
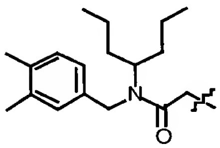
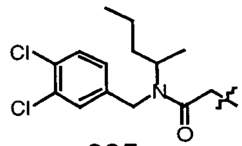
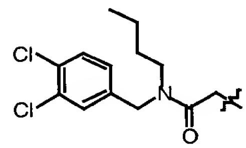
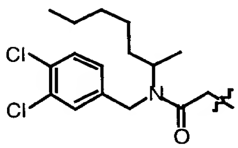
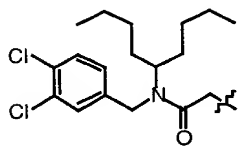
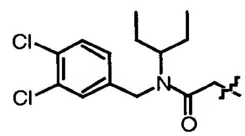
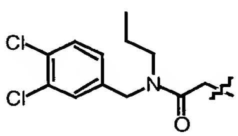
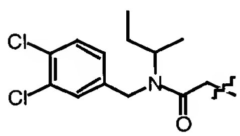
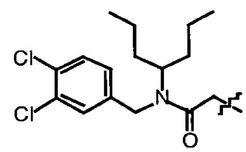
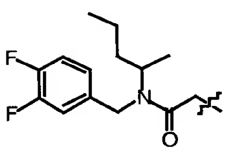
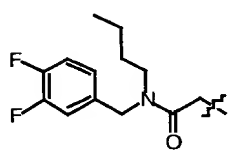
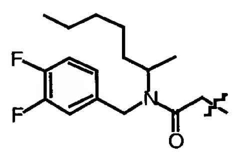
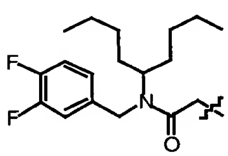
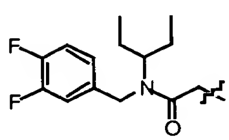
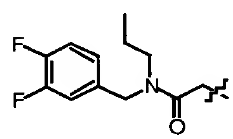
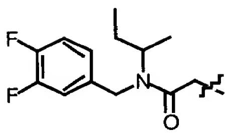
 391.	 392.	 393.
 394.	 395.	 396.
 397.	 398.	 399.
 400.	 401.	 402.
 403.	 404.	 405.
 406.	 407.	 408.

Table 3B cont.

R **R** **R**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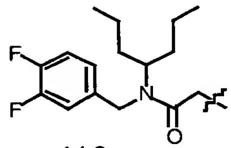
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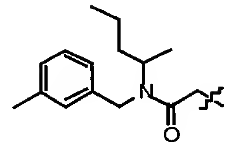
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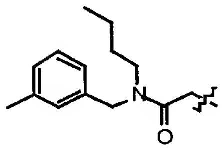
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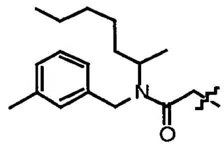
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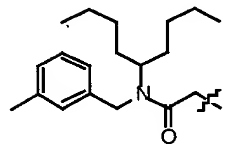
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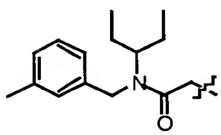
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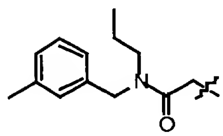
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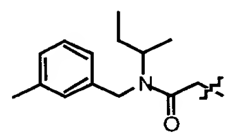
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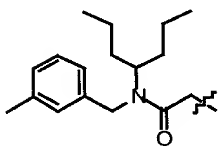
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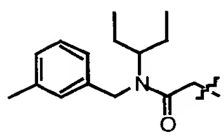
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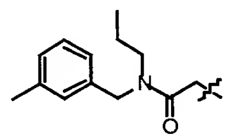
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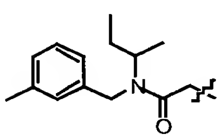
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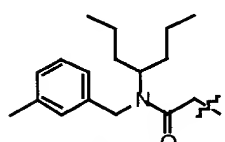
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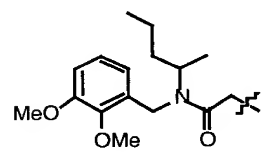
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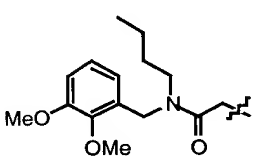
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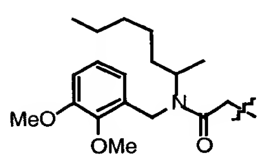
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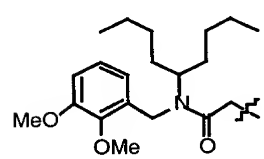
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Table 3B cont.

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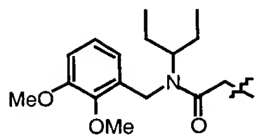
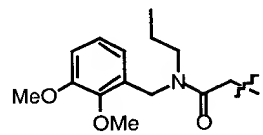
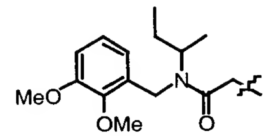
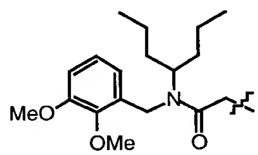
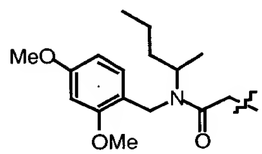
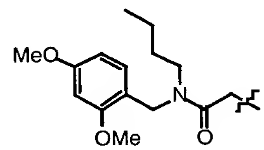
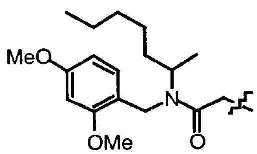
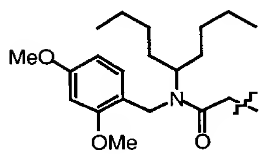
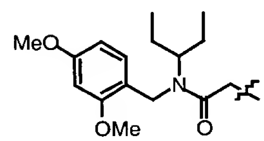
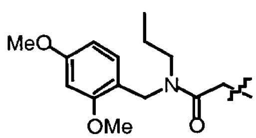
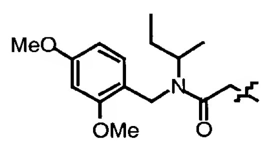
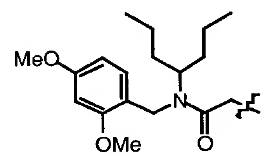
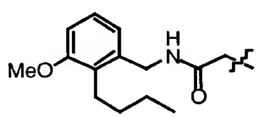
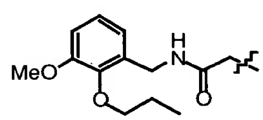
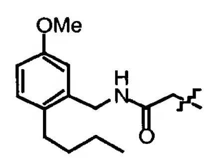
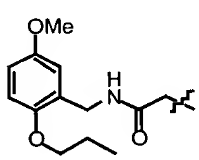
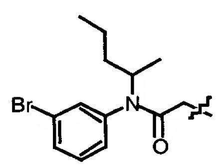
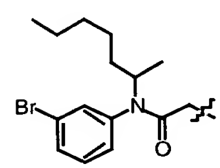
 427.	 428.	 429.
 430.	 431.	 432.
 433.	 434.	 435.
 436.	 437.	 438.
 439.	 440.	 441.
 442.	 443.	 444.

Table 3B cont.

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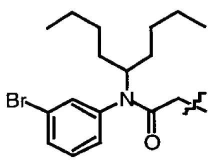
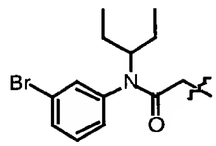
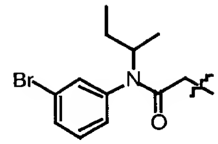
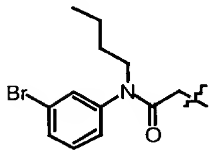
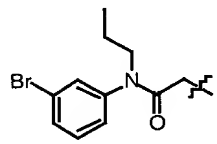
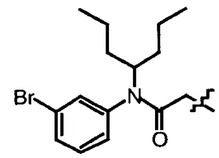
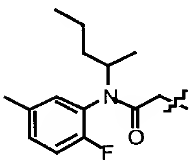
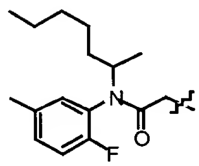
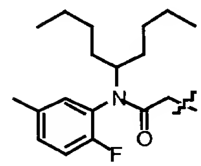
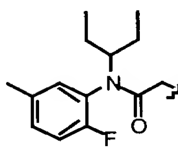
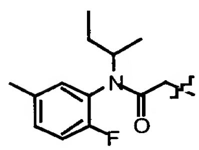
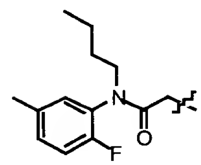
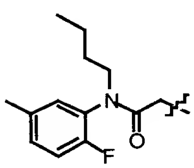
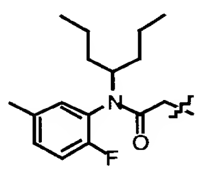
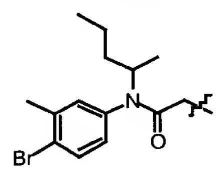
 445.	 446.	 447.
 448.	 449.	 450.
 451.	 452.	 453.
 454.	 455.	 456.
 457.	 458.	 459.

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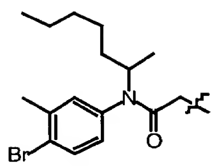
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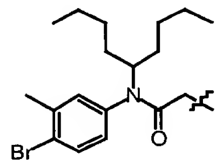
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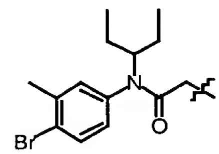
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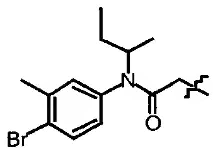
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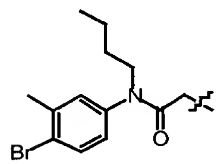
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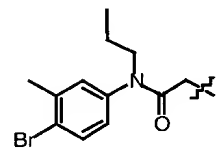
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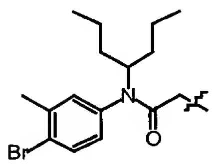
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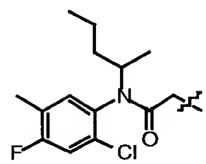
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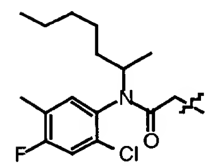
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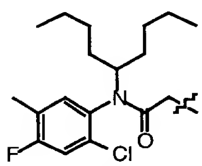
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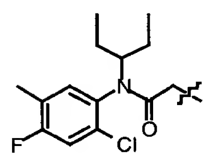
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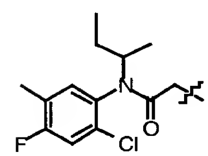
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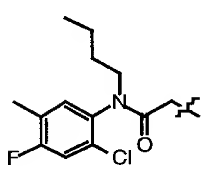
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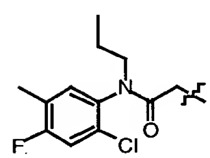
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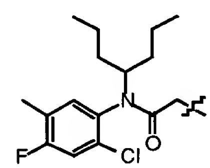
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Table 3B cont.

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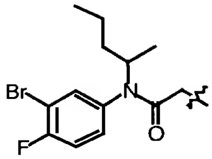
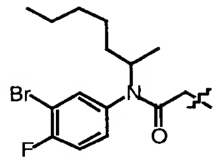
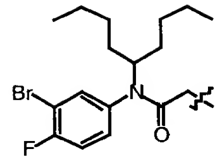
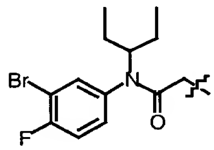
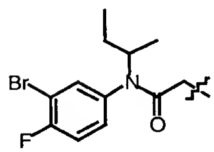
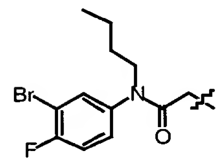
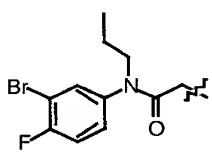
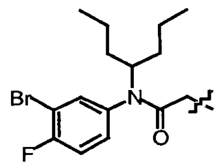
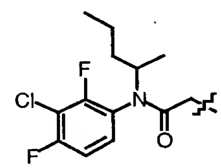
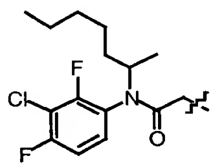
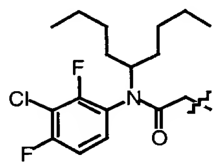
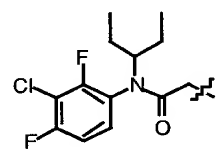
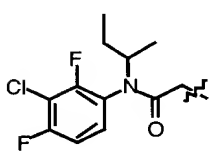
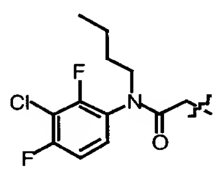
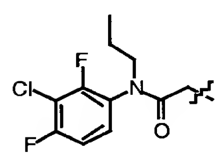
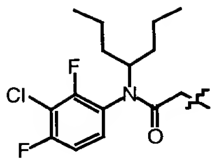
 475.	 476.	 477.
 478.	 479.	 480.
 481.	 482.	 483.
 484.	 485.	 486.
 487.	 488.	 489.

Table 3B cont.

R **R** **R**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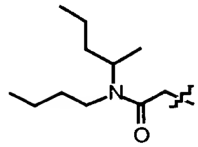
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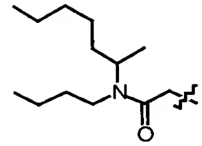
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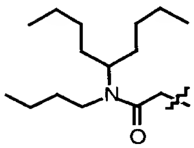
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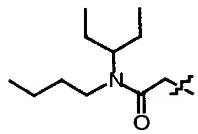
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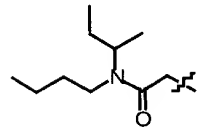
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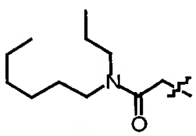
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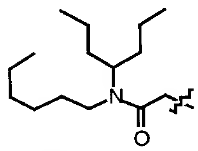
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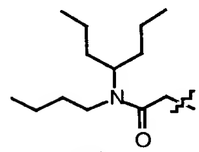
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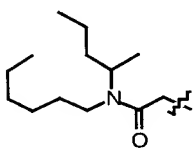
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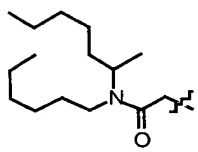
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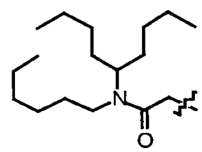
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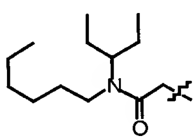
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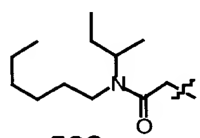
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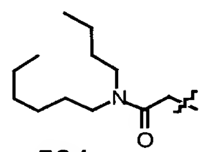
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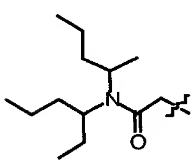
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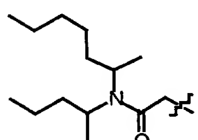
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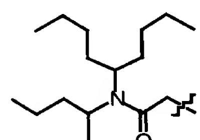
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Table 3B cont.

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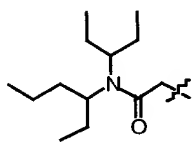
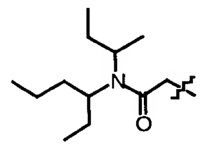
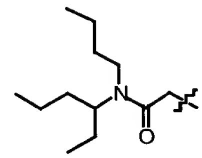
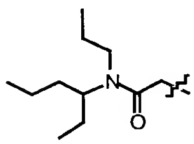
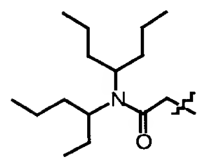
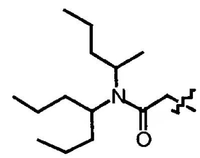
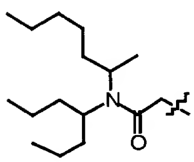
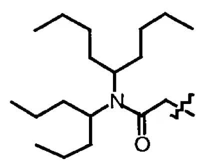
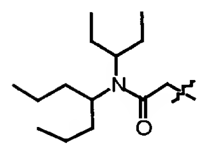
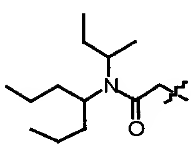
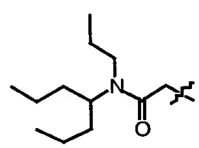
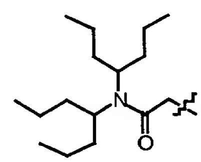
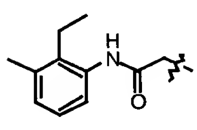
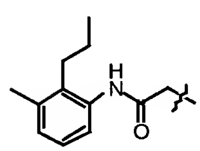
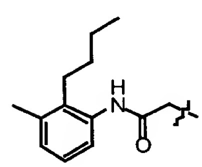
 508.	 509.	 510.
 511.	 512.	 513.
 514.	 515,	 516.
 517.	 518.	 519.
 520.	 521.	 522.

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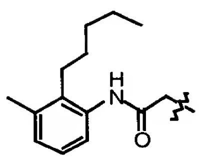
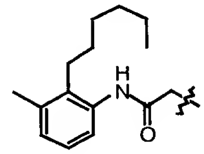
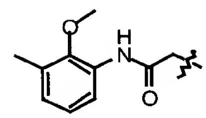
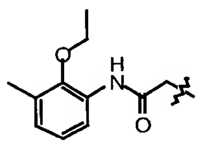
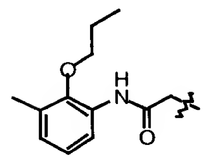
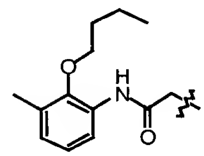
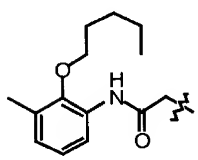
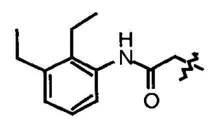
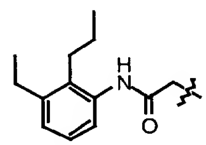
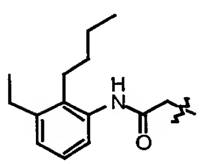
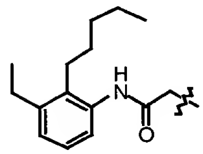
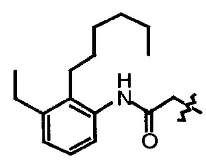
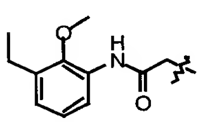
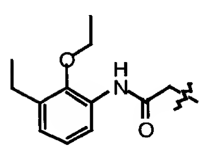
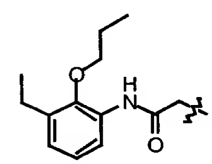
 523.	 524.	 525.
 526.	 527.	 528.
 529.	 530.	 531.
 532.	 533.	 534.
 535.	 536.	 537.

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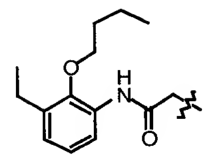
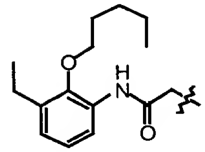
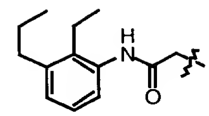
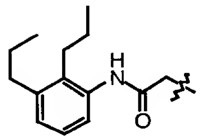
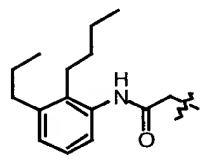
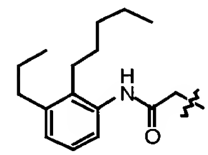
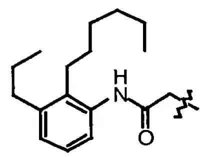
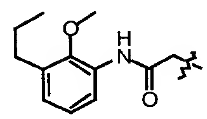
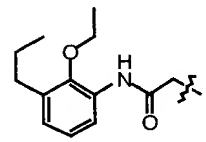
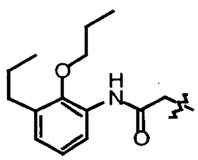
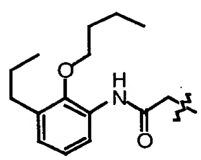
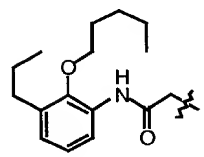
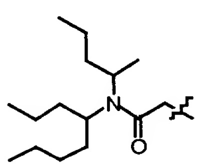
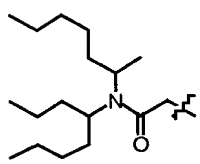
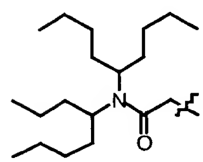
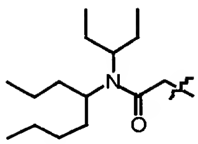
 538.	 539.	 540.
 541.	 542.	 543.
 544.	 545.	 546.
 547.	 548.	 549.
 550.	 551.	 552.

Table 3B cont.

R **R** **R**



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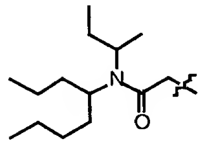

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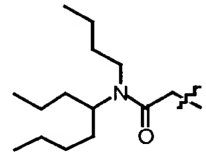

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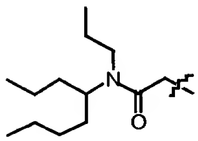

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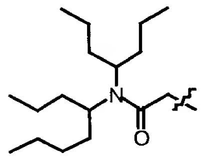

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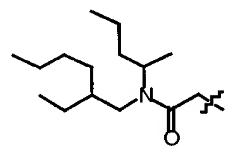

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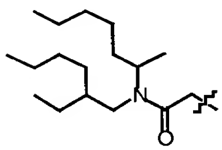

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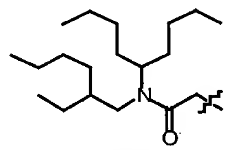

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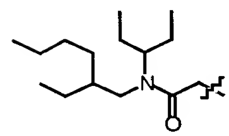

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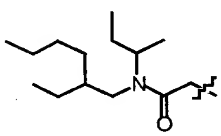

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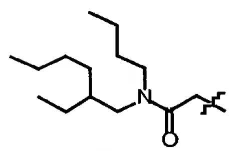

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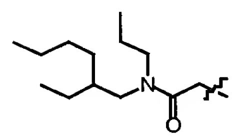

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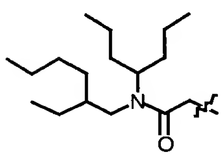

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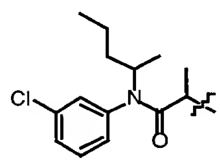

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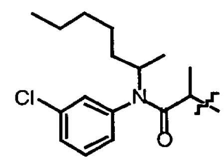

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Table 3B cont.

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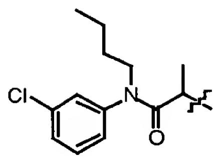
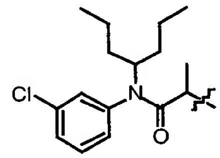
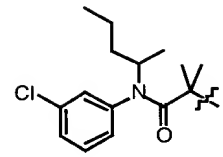
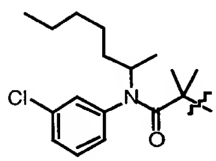
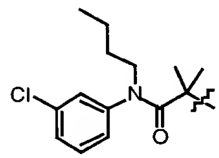
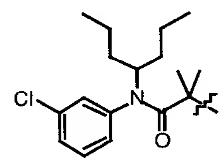
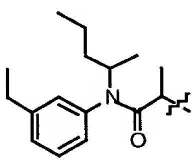
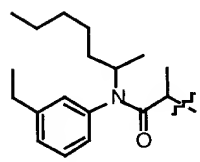
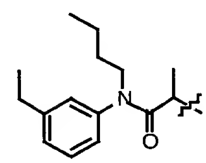
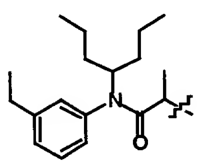
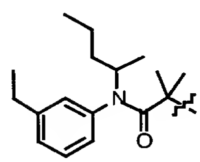
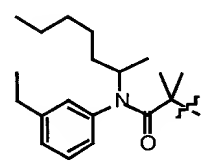
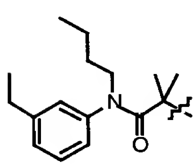
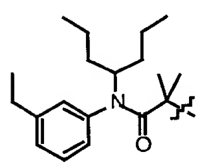
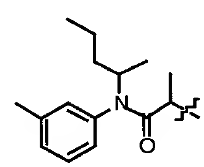
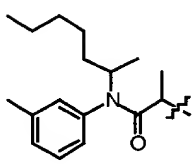
 568.	 569.	 570.
 571.	 572.	 573.
 574.	 575.	 576.
 577.	 578.	 579.
 580.	 581.	 582.

Table 3B cont.

R	R	R



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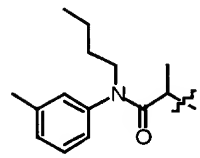

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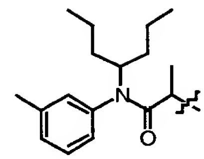

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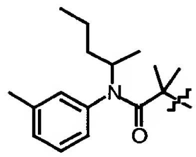

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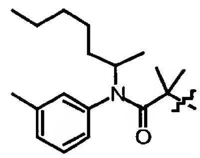

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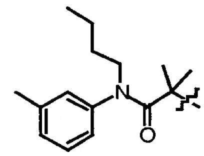

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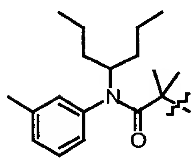
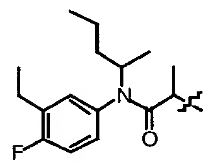
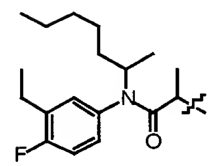


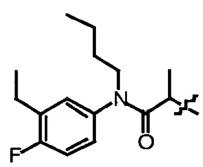
589.



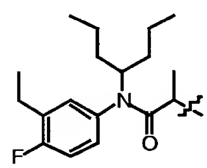
590.



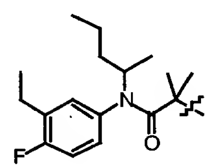
591.



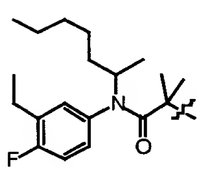
592.



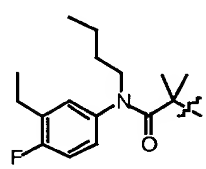
593.



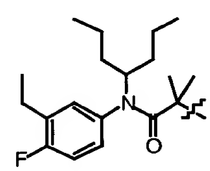
594.



595.



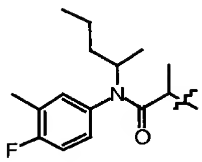
596.



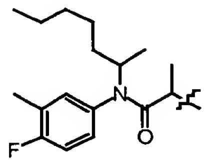
597.

Table 3B cont.

R **R** **R**



598.



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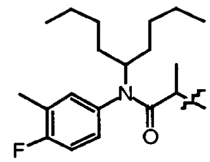
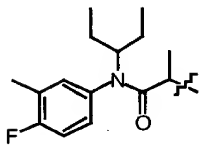
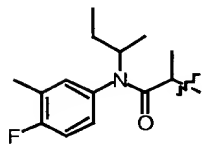


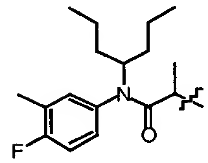
600.



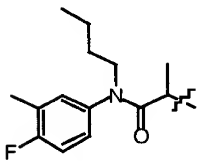
601.



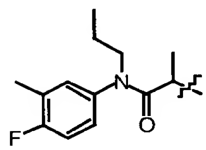
602.



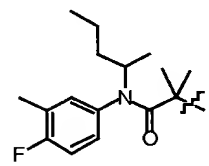
603.



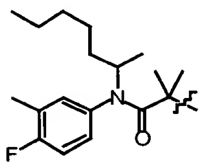
604.



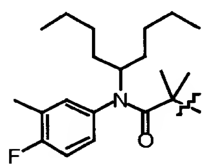
605.



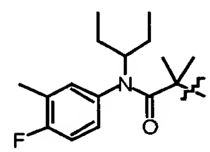
606.



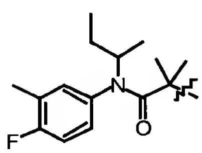
607.



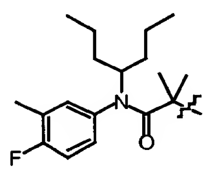
608.



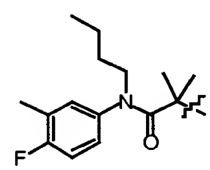
609.



610.



611.



612.

Table 3B cont.

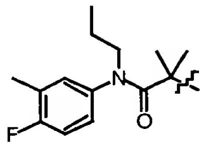
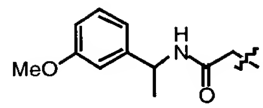
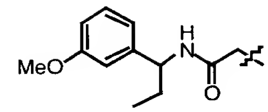
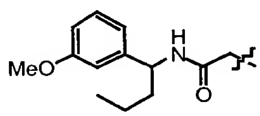
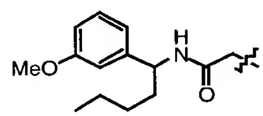
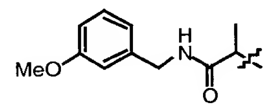
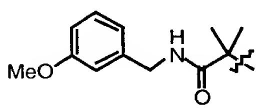
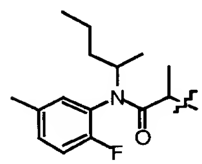
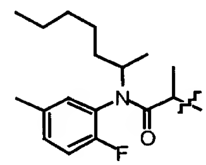
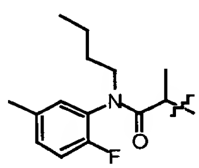
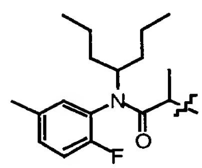
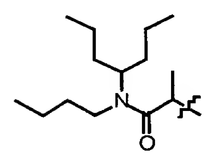
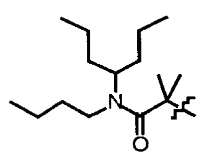
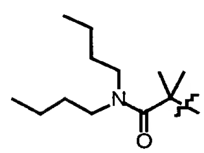
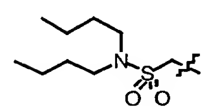
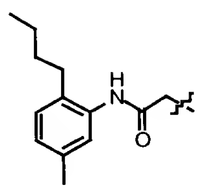
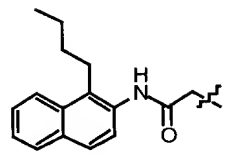
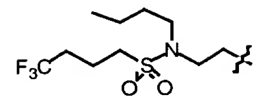
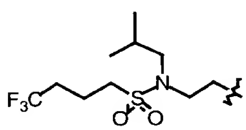
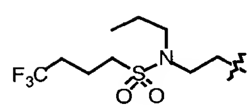
R	R	R
 613.	 614.	 615.
 616.	 617.	 618.
 619.	 620.	 621.
 622.	 623.	 624.
 625.	 626.	 627.

Table 3B cont.

R	R	R
		
628.	629.	630.
		
631.	632.	

Example 340

***trans,trans*-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-(3-methylbut-1-yl)-N-phenyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid**

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.85 (d, J=6 Hz, 6H), 1.25 (q, J=7 Hz, 2H), 1.42-1.56 (m, 1H), 3.43-3.85 (m, 9H), 3.88s (3), 5.95 (s, 2H), 6.80 (d, J=7 Hz, 1H), 6.86 (dd, J=9 Hz, 1H), 6.89-7.00 (m, 2H), 6.97 (d, J=1 Hz, 1H), 7.04 (d, J=9 Hz, 2H), 7.37 (d, J=9 Hz, 2H), 7.40-7.47 (m, 3H). MS (C.I.) m/e C (53.12, 53.11), H (4.63, 4.80), N (3.33, 3.28).

Example 341

***trans, trans*-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(N-butyl-N-(4-methylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid**

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=7 Hz, 3H), 1.20-1.47 (m, 4H), 2.37 (s, 3H), 2.83 (q, J=7 Hz, 2H), 3.06-3.25 (m, 2H), 3.40-3.50 (m, 1H), 3.51-3.63 (m, 3H), 3.80 (s, 3H), 3.87 (d, J=9 Hz, 1H), 5.92 (s, 2H), 6.74 (d, J=8 Hz, 1H), 6.80-6.86 (m, 3H), 6.89 (d, J=8 Hz, 2H), 7.04 (d, J=2 Hz, 1H), 7.12 (d, J=8 Hz, 2H), 7.19

(d, J=8 Hz, 2H). MS (DCI) m/e 545 $(M+H)^+$. Analysis calcd for $C_{32}H_{36}N_2O_6$: C, 70.57; H, 6.66; N, 5.14. Found: C, 70.20; H, 6.81; N, 5.03.

Example 342

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-propoxyphenyl)-1-(N,N-di(n-butyl)amino)carbonyl)methyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H (300MHz, $CDCl_3$) δ 7.30 (2H, d, J=9), 7.03 (1H, d, J=2), 6.83 (3H, m), 6.72 (1H, d, J=9), 5.95 (1H, d, J=2), 5.93 (1H, d, J=2), 3.88 (2H, t, J=7), 3.73 (1H, d, J=12), 3.58 (1H, m), 3.53-3.20 (4H, m), 3.10-2.90 (4H, m), 2.72 (1H, d, J=15), 1.79 (2H, q, J=8), 1.50-1.05 (8H, m), 1.02 (3H, t, J=7), 0.87 (3H, t, J=7), 0.80 (3H, t, J=7). MS (DCI/NH_3) m/e 539 $(M+H)^+$. Anal calcd for $C_{31}H_{42}N_2O_6 \cdot 0.5H_2O$: C, 67.98; H ,7.91; N, 5.11. Found: C,68.24; H, 7.70; N, 5.03.

Example 343

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-propylphenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^1H (300MHz, $CDCl_3$) δ 7.31(2H, d, J=9), 7.13 (2H, d, J=9), 7.03 (1H, d, J=2), 6.84 (1H, dd, J=6, 2), 6.73 (1H, d, J=9), 5.95 (1H, d, J=2), 5.93 (1H, d, J=2), 3.76 (1H, d, J=10), 3.60 (1H, m), 3.55-3.20 (4H, m), 3.13-2.88 (4H, m), 2.75 (1H, d, J=15), 2.55 (2H, t, J=8),1.62 (2H, q, J=8), 1.50-1.00 (8H, m), 0.92 (3H, t, J=7), 0.85 (3H, t, J=7), 0.78 (3H, t, J=7). MS (DCI/NH_3) m/e 523 (MH^+). Anal calcd for $C_{31}H_{42}N_2O_5 \cdot 0.25\ H_2O$: C, 70.63; H, 8.13; N, 5.31. Found: C, 70.55; H, 8.08; N, 5.18.

Example 344

trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3-(N-propyl-N-*n*-pentanesulfonylamino)propyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 316, the title compound was prepared. ^1H NMR (300MHz, $CDCl_3$) δ 0.85 (t, J=7Hz, 3H), 0.90 (t, J=7Hz, 3H), 1.3-1.4 (m, 4H), 1.5-1.6 (sextet, J=7, 2H), 1.65-1.8 (m, 4H), 2.05-2.15 (m, 1H), 2.43-2.56 (m, 1H), 2.72-3.1 (m, 7H), 3.27-3.4 (m, 2H), 3.5-3.6 (m, 2H), 3.80 (s, 3H), 5.95 (s, 2H), 6.73 (d, J=8Hz, 1H), 6.8-6.9 (m, 1H), 6. 85 (d, J= 9Hz, 2H), 7.02 (d, J=2Hz, 1H), 7.80 (d, J=9Hz, 2H).

Example 345

trans,trans-4-(1,2-Dihydrobenzofuran-5-yl)-2-(4-ethylphenyl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H (300MHz, $CDCl_3$) δ 7.40 (3H, m), 7.22 (2H, d, J=8), 7.13 (1H, dd, J=8, 3), 6.72 (1H, d, J=9), 5.28 (1H, d, J=12), 4.55 (2H, t, J=9), 4.15 (1H, d, J=18), 4.03 (2H, m), 3.75 (2H, m), 3.40 (2H, m), 3.20 (2H, t, J=9), 3.15 (1H, m), 3.10-2.90 (2H, m), 2.63 (2H, q, J=9), 1.47 (2H, m), 1.31 (4H, m), 1.12 (3H, t, J=8), 1.10 (2H,m), 0.92 (3H, t, J=9), 0.80 (3H, t, J=9). MS (DCI/NH_3) m/e 507 (M+H$^+$). Anal calcd for $C_{31}H_{42}N_2O_4 \cdot 1.0$ TFA: C ,63.86 ; H, 6.98; N, 4.51. Found: C, 63.95; H, 7.12; N, 4.43.

Example 346

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-(3-pentyl)-N-phenylamino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.93 (t, J=7.3 Hz, 3H), 0.94 (t, J=7.3 Hz, 3H), 1.33 (m, 4H), 2.72 (d, J=15.2 Hz, 1H), 2.81 (m, 1H), 3.11-3.23 (m, 2H), 3.45-3.57 (m, 2H), 3.79 (s, 3H), 3.83 (d, J=9.8 Hz, 1H), 4.54 (m, 1H), 5.92 (s, 2H), 6.73 (d, J=7.8 Hz, 1H), 6.83 (m, 3H), 6.98 (bs, 2H), 7.04 (d, J=1.7 Hz, 1H), 7.07 (2), 7.37 (m, 3H). MS (DCI) m/e 545 (M+H$^+$). Anal calcd for $C_{32}H_{33}N_2O_6 \cdot 0.35H_2O$: C, 69.76; H, 6.71; N, 5.08. Found: C, 69.72; H, 6.66; N, 4.94.

Example 347

trans,trans-4-(1,3-Benzodioxol-5-yl)-2-(4-methoxyphenyl)-1-(((N-butyl)-N-(3-trifluoromethylphenyl)amino)carbonyl)methyl)pyrrolidine-3-carboxylic acid

Using the procedures described in Example 1, the title compound was prepared. ^{1}H NMR (300 MHz, CD_3OD) δ 0.87 (t, J=6.6 Hz, 3H), 1.17-1.45 (m, 4H), 2.65 (d, J=16.5 Hz, 1H), 2.72 (m, 1H), 3.10 (t, J=9.5 Hz, 1H), 3.21-3.27 (m, 1H), 3.40 (dd, J=4.1, 9.9 Hz, 1H), 3.54 (m, 1H), 3.61-3.74 (m, 3H), 3.77 (s, 3H), 5.93 (s, 2H), 6.73-6.85 (m, 4H), 7.02 (m, 3H), 7.33 (d, J=7.5 Hz, 1H), 7.40 (s, 1H), 7.58 (t, J=7.8 Hz, 1H), 7.69 (d, J=7.5 Hz, 1H). MS (DCI) m/e 599 (M+H$^+$). Anal calcd for $C_{32}H_{33}F_3N_2O_6$: C, 64.21; H, 5.56; N, 4.68. Found: C, 64.09; H, 5.63; N, 4.57.

Example 348